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Iron Deficiency and Anemia in Heart Failure

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CONTENTS March / *Mart* 2017 İÇİNDEKİLER

Dear Colleagues,

Management of comorbidities constitutes an important part of treatment in heart failure (HF). HF is a clinical syndrome where the incidence and prevalence gradually increase with age. Advanced age is associated with increased incidence rates of comorbidities such as hypertension, diabetes, coronary artery disease, hyperlipidemia, atrial fibrillation, chronic obstructive pulmonary disease, renal impairment, degenerative valvular disease, and sleep apnea. Registry studies indicate that only 4% of HF patients over 65 years of age are free of comorbidities while 40% have ≥5 comorbid conditions. The recently published data of Heart Failure Long Term Registry including 12,440 cases demonstrated presence of hypertension in 58% of the patients with HF, ischemic heart disease in 43%, atrial fibrillation in 37%, diabetes in 32%, renal dysfunction in 18% and chronic obstructive pulmonary disease in 14%. The rates are even higher among patients hospitalized due to acute HF. Comorbidities are more common in heart failure with preserved ejection fraction as the patients are older, and management of comorbidities presents the mainstay of treatment in these patients.

Comorbidities complicate symptomatic control in heart failure, interfere with quality of life, worsen the clinical course, and increasehospitalization rates as well as mortality. Furthermore, certain comorbidities such as renal dysfunction and chronic obstructive pulmonary disease also interfere with evidence based treatment of HF. Similarly, the clinical course of HF may be disrupted further due to some medications used for the treatment of comorbid conditions (calcium channel blockers, glitazones, NSAIDs, inhaled beta-mimetics, steroids etc.). Therefore, HF guidelines strongly emphasize the fact that adequate control and management of comorbidities is an essential aspect of HF treatment.

Iron deficiency and anemia are among the most commonly seen comorbidities in HF. Data obtained from studies indicate that approximately half of the patients with HF have iron deficiency and/or anemia. Historically, iron deficiency and anemia have been shown to be strongly associated with the severity and prognosis of HF, and since the evidence obtained in recent years indicate clinical benefits with relevant treatment in HF, the treatment of iron deficiency and anemia in HF has become a subject of interest. The clinical benefits demonstrated in small studies with erythropoiesis stimulating agents were not subsequently confirmed in major studies; furthermore, thromboembolic events were shown to be increased with these agents, leading to disappointment. However, although improved mortality has not been demonstrated, major studies on intravenous iron therapy have shown improvement in quality of life, NYHA class, 6-minute walking distance, peak oxygen consumption and HF hospitalization rates in patients with iron deficiency with or without anemia, making intravenous iron therapy a treatment target in HF. In 2016, the ESC guidelines on HF were the first to include intravenous iron administration as a standard recommendation for patients with HF.

This document prepared as a guide by professionals with knowledge and expertise in their fields provides a comprehensive discussion on iron deficiency and anemia in HF, and evaluates the relevant approaches for management and treatment in current clinical practice in light of the currently available evidence.

It is our hope that this document provided by the Heart Failure Working Group of Turkish Society of Cardiology will serve as a useful guide for healthcare professionals.

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ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACEi	Angiotensin converting enzyme inhibitor
AHA	American Heart Association
AHF	Acute heart failure
ARB	Angiotensin receptor blocker
WBC	White blood cell
BNP	Brain natriuretic peptide
CI	Confidence interval
ID	Iron deficiency
HFrEF	Heart failure with reduced ejection fraction
DPG	2,3 diphosphoglycerate
WHO	World Health Organization
M	Male
EF	Ejection fraction
EHFS-II	Euro Heart Failure Survey II
EMA	European Medicines Agency
EQ-5D	European Quality of Life–5 Dimensions
ESA	Erythropoiesis stimulating agent
ESC	European Society of Cardiology
Fe	Iron
FCM	Ferric carboxymaltose
FDA	Food and Drug Administration
GIS	Gastrointestinal system
GFR	Glomerular filtration rate
Hb	Hemoglobin
HFSA	Heart Failure Society of America
HLA	Human leukocyte antigen
Htc	Hematocrit
IL	Interleukin
ISC	Iron sucrose
IV	Intravenous
F	Female
KCCQ	Kansas City Cardiomyopathy Questionnaire
HFpEF	Heart failure with preserved ejection fraction
Cr	Creatinine
CrCl	Creatinine clearance
HF	Heart failure
CV	Cardiovascular
LVEF	Left ventricular ejection fraction
MLHFQ	Minnesota Living With Heart Failure Questionnaire
NYHA	New York Heart Association
NO	Nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OR	Odds ratio
PGA	Patient Global Assessment
RCT	Randomized clinical trial
RR	Relative risk
sTfR	Soluble transferrin receptor
TIBC	Total iron binding capacity
TNF	Tumor necrosis factor
TSAT	Transferrin saturation
VO2	Peak O_2 consumption
ND	No data

ACRONYMS OF CLINICAL STUDIES

AFFIRM-AHF	Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency
ADHERE	Acute Decompensated Heart Failure National Registry
ARIC	Atherosclerosis Risk in Communities
COMET	Carvedilol or Metoprolol European Trial
CONFIRM-HF	Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure
CHARM	The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity
FAIR-HF	Ferinject Assessment in Patients With IRon Deficiency and Chronic Heart Failure
FERRIC-HF	Ferric Iron Sucrose in Heart Failure
IRONOUT-HF	the Oral Iron Repletion effects on Oxygen UpTake in Heart Failure trial
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure
RED-HF	Treatment of anemia with darbepoetin alfa in systolic heart failure
SENIORS	The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure
SOLVD	Studies on Left Ventricular Dysfunction
STAMINA HeFT	The Study of Anemia in Heart Failure Trial
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
Val-HEFT	Valsartan in Heart Failure Trial

Iron deficiency and anemia in heart failure

Kalp yetersizliğinde demir eksikliği ve anemi

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ABSTRACT

Heart failure is an important community health problem. Prevalence and incidence of heart failure have continued to rise over the years. Despite recent advances in heart failure therapy, prognosis is still poor, rehospitalization rate is very high, and quality of life is worse. Comorbidities in heart failure have negative impact on clinical course of the disease, further impair prognosis, and add difficulties to treatment of clinical picture. Therefore, successful management of comorbidities is strongly recommended in addition to conventional therapy for heart failure. One of the most common comorbidities in heart failure is presence of iron deficiency and anemia. Current evidence suggests that iron deficiency and anemia are more prevalent in patients with heart failure and reduced ejection fraction, as well as those with heart failure and preserved ejection fraction. Moreover, iron deficiency and anemia are referred to as independent predictors for poor prognosis in heart failure. There is strong relationship between iron deficiency or anemia and severity of clinical status of heart failure. Over the last two decades, many clinical investigations have been conducted on clinical effectiveness of treatment of iron deficiency or anemia with oral iron, intravenous iron, and erythropoietin therapies. Studies with oral iron and erythropoietin therapies did not provide any clinical benefit and, in fact, these therapies have been shown to be associated with increase in adverse clinical outcomes. However, clinical trials in patients with iron deficiency in the presence or absence of anemia have demonstrated considerable clinical benefits of intravenous iron therapy, and based on these positive outcomes, iron deficiency has become target of therapy in management of heart failure. The present report assesses current approaches to iron deficiency and anemia in heart failure in light of recent evidence.

Keywords: Anemia; heart failure; iron deficiency.

ÖZET

Kalp yetersizliği, insidans ve prevalansı giderek artan önemli bir toplum sağlığı problemidir. Tedavide sağlanan ilerlemelere rağmen halen yaşam kalitesi düşük, hastaneye yatış oranları yüksek ve prognoz kötüdür. Kalp yetersizliğine eşlik eden hastalıklar klinik seyri olumsuz etkilemekte, prognozu kötüleştirmekte, tedaviyi güçleştirmekte ve klinik tablonun kontrolünü zorlaştırmaktadır. Bu nedenle kalp yetersizliğine yönelik tedavi ile birlikte komorbid durumların tedavisi ve kontrolünün sağlanması önemle vurgulanmaktadır. Kalp yetersizliğinde en sık rastlanan komorbid durumlardan biri demir eksikliği ve anemidir. Mevcut veriler demir eksikliği ve aneminin hem düşük ejeksiyon fraksiyonlu hem de korunmuş ejeksiyon fraksiyonlu kalp yetersizliğinde yaygın olduğunu göstermektedir. Aynı zamanda kalp yetersizliğinde demir eksikliği ve anemi kötü prognoz için bağımsız prediktörler olarak bulunmaktadır. Ayrıca demir eksikliği ve aneminin klinik tablonun ciddiyeti ile güçlü bir ilişkisi söz konusudur. Son yıllarda komorbid durum olarak demir eksikliği ve/veya aneminin eritropoietin, oral demir veya intravenöz demir ile tedavisiyle kalp yetersizliğinde klinik yarar sağlanıp sağlanamayacağına ilişkin çalışmalar yapılmıştır. Eritropoietin ve oral demir ile yapılan çalışmalarda beklenen klinik yararlar sağlanamamış ve istenmeyen olaylarda artış gözlenmiştir. Anemi olsun olmasın demir eksikliği bulunan kalp yetersizliği olgularında intravenöz demir tedavisi ile yapılan çalışmalarda mortalitede olmasa bile klinik sonuçlarda anlamlı yararların gösterilmesi kalp yetersizliğinde demir eksikliğini tedavi hedefi konumuna getirmiştir. Rehber niteliğinde hazırlanan bu belgenin amacı, kalp yetersizliğinde demir eksikliği ve anemiye yaklaşımı güncel kanıtlar eşliğinde değerlendirmektir.

Anahtar sözcükler: Anemi; kalp yetersizliği; demir eksikliği.

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1.0 INTRODUCTION – Yüksel Çavuşoğlu

Heart failure (HF) is a clinical syndrome accompanied by comorbidities. The most commonly seen comorbid conditions include hypertension, coronary artery disease, chronic renal impairment, diabetes, chronic obstructive pulmonary disease, and respiratory sleep apnea. In recent years, increasing evidence have shown that iron deficiency and anemia are common in patients with HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and in patients with acute HF. Discovery of the notion that iron deficiency and anemia are independent predictors of poor prognosis in HF led to increased interest regarding iron deficiency and anemia in HF. The clinical benefits shown with treatment for iron deficiency and anemia have brought a new dimension to this field by drawing attention of healthcare professionals. This document prepared to serve as a guide aims to evaluate the questions, concerns and solutions likely to be encountered during everyday clinical practice regarding iron deficiency and anemia in HF based on the currently available evidence.

2.0 DEFINITION, POTENTIAL CAUSES, CLINICAL FEATURES – Yüksel Çavuşoğlu

2.1 What is the definition and importance of iron deficiency and anemia in heart failure?

Iron deficiency and anemia are among the most commonly seen comorbidities in heart failure. When defined according to World Health Organization criteria (hemoglobin <13 g/dL in men, <12 g/dL in women), anemia is present approximately in 1/3 of patients with HF. Anemia prevalence was reported as 37.2% in a meta-analysis including 153,180 patients with HF.[1] This rate decreases to nearly 20% in clinical studies on HF as patients with severe anemia and serious renal dysfunction are excluded from the clinical studies; however, a prevalence of anemia of up to 49% is observed in patients hospitalized due toacute decompensated HF.[2] These figures indicate that anemia is a significant problem in HF. Anemia has become an important consideration and a treatment target in HF during the last 2 decades upon being associated with the severity of HF as well as serving as a prognostic indicator.

The prevalence of iron deficiency with or without anemia is reported to be 37%-61% in HF.[3] These figures indicate a higher incidence rate for iron deficiency with or without anemia compared to the prevalence of anemia. Furthermore, iron deficiency has been identified as a marker of poor prognosis regardless of the anemia status.[4] Mortality is increased by 4-fold in patients with iron deficiency with or without anemia compared to those without iron deficiency.[5] These findings indicate that iron deficiency is a stronger prognostic marker than anemia. In recent years, studies on intravenous (IV) iron therapy have shown significant benefits in clinical outcomes (improved quality of life, improvement in NYHA class, increase in 6-minute walking distance, increased peak oxygen consumption, decreased HF hospitalization) if not in mortality, highlighting the importance of iron deficiency treatment in HF, followed by the inclusion in ESC guidelines on HF as a target of treatment for the first time in 2016.[5,6]

2.2 Are iron deficiency and anemia different conditions in heart failure?

Iron deficiency in HF is defined as ferritin levels <100 μg/L or transferrin saturation (TSAT) <20% if the ferritin level is 100-299 μg/L.[5,6] On the other hand, anemia is defined as hemoglobin values <13 g/dL in men and <12 g/dL in women as per the World Health Organization criteria. Presence of anemia is not necessarily required for iron deficiency. In other words, iron deficiency may be present without anemia. Iron deficiency was found in 37% of all patients included in a prospective observational series of 546 patients with HFrEF while the rate was 57% and 32% among anemic and non-anemic patients, respectively.[4] The analysis of the largest international patient pool to date (n=1506, patients HFrEF and HFpEF) has revealed iron deficiency in 50% of all HF patients while this rate was reported as 61% in anemic HF patients and 46% in non-anemic HF patients.[7] These findings indicate that a significant portion of HF patients without anemia are in fact iron-deficient.

2.3 What are the causes and potential mechanisms of iron deficiency and anemia in heart failure?

The causes and potential mechanisms of iron deficiency and anemia in HF are considered complex and multi-factorial. The most commonly highlighted causes include inflammatory activation, malnutriti-

on, renal impairment, hemodilution, diabetes, impaired bone marrow function, receiving an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and occult bleeding in the gastrointestinal system (GIS)[8–10] (Table 1).

Inadequate nutrition, decreased iron absorption and occult blood loss in GIS are the first scenarios to consider regarding the causes and potential mechanisms of iron deficiency. Conditions such as intestinal edema, loss of appetite and cachexia result in impaired iron intake due to inadequate nutrition, particularly with the progression of HF.[8–10] As the underlying cause in 2/3 of patients with HF is coronary artery disease requiring co-administration of aspirin and other antiplatelet agents, such treatment is known to be associated with chronic blood loss in GIS.

Increased inflammatory activation in heart failure leads to elevated hepcidin levels in the liver.[2,3,8–10] Hepcidin is a protein which blocks intestinal iron intake by means of ferroportin inhibition. Hepcidin production is stimulated by cytokines such as interleukin (IL)-6 and IL-1 and tumor necrosis factor-alpha (TNF-alpha). Increased hepcidin reduces intestinal iron intake. Furthermore, hepcidin decreases the release of iron by macrophages, thereby leading to reduced levels of available iron. Elevated pro-inflammatory cytokines (TNF-alpha, IL-6, IL-1, IL-18) do not only increase hepcidin levels but also decrease renal erythropoietin secretion, suppress erythropoietin activity in the bone marrow and lead to reduced iron reservoirs in heart failure.[2,3,8–10]

Renal dysfunction is present in 20-25% of patients with heart failure and contributes to anemia development by reducing erythropoietin production in the kidney. Anemia risk is increased by 3-fold in HF patients with GFR <60 mL/min/1.73 m^2.[11] ACEi/ARBs constitute the mainstay of treatment in HF and contribute to anemia development by suppressing erythroid progenitor cell development and by reducing the levels and blocking the function of angiotensin, which normally induces erythropoietin production.[8–10]

While reported evidence demonstrate that the congestion and hypervolemia observed in HF patients result in dilutional anemia,[12] it should also be noted that hemodilution may be involved in anemia development mechanisms, particularly in patients hospitalized for acute decompensated HF and patients with advanced HF. In fact, anemia prevalence is reported to be higher among patients hospitalized for acute decompensated HF compared to HF patients in the outpatient setting, with anemic parameters which may return to normal upon resolving the congestion.[12,13] For diabetic patients, the glycosylation-related damage on erythropoietin-producing cells in the kidney is thought to contribute to anemia in HF patients by reducing erythropoietin production. Indeed, lower hemoglobin levels are reported among diabetic patients compared to non-diabetics.[10]

2.4 What are the clinical features associated with iron deficiency and anemia in heart failure?

Anemic HF patients are often older, female, cachectic subjects with advanced HF presentation, renal dysfunction and concurrent diabetes (Table 2). There is a close, well-established association between

Table 1. Mechanisms of iron deficiency and anemia in heart failure

Increased inflammatory cytokines
Increased hepcidin
Renal impairment and decreased erythropoietin production
Receiving ACEi/ARB
Malnutrition
Occult bleeding in the gastrointestinal tract
Hemodilution
Diabetes
Impaired bone marrow function

Table 2. Clinical features associated with iron deficiency and anemia in heart failure

Advanced age
Female gender
Low body mass index
NYHA III-IV
Increased natriuretic peptide
Elevated C-reactive protein
Renal dysfunction
Diabetes
Peripheral edema
High-dose diuretic use

the severity of HF and anemia.[2–4] Anemia incidence rates are known to increase with worsening NYHA classes.[2–4] Female gender, elevated BNP and plasma C-reactive protein levels are closely associated with anemia.[4] Furthermore, anemia is also associated with clinical characteristics of advanced HF such as peripheral edema, increased creatinine, low GFR and potassium levels, use of high-dose diuretics, hyponatremia and low body mass index.[2,11] While anemia prevalence is somewhat higher among middle-aged women compared to men, higher prevalence rates are observed in men with advanced age.[2,11]

Chronic renal disease is anindependent and strong predictor of anemia. Anemia levels worsen proportionally with the degree of renal dysfunction.[2,11] In patients with GFR <60 mL/min/1.73 m^2, a 0.29 gr/dL drop in hemoglobin level is reported with each 10 mL decrease in GFR.[14] Additionally, cachexia and anemia are linked as an indicator of clinical worsening in HF, and increasing anemia rates are seen with decreased body mass index. Anemia prevalence is higher among diabetic patients compared to non-diabetics.[15] Furthermore, the frequency of diabetes is reported to be higher in anemic subjects compared to non-anemic patients.

Prevalence of anemia is reported to be similar among patients with HFrEF and HFpEF. The CHARM study found anemia in 27% of the patients with HFpEF and in 25% of patients with HFrEF.[14] Anemia prevalence is known to increase with worsening diastolic dysfunction. However, it should be taken into account that the age factor and greater number of comorbidities in HFpEF may also contribute to higher prevalence in this group. A weak correlation is reported between EF and hemoglobin levels.[16]

3.0 PREVALENCE – Tolga Sinan Güvenç

3.1 How common are iron deficiency and anemia in heart failure?

As with all other diseases, the prevalence and incidence of anemia and iron deficiency in chronic HF eventually depends on how these three disorders (HF, anemia and iron deficiency) were defined. The available data often show the extent of anemia and iron deficiency in HFrEF as majority of retrospective analyses on observational studies and randomized controlled trials included a left ventricular ejection fraction of less than 35% or 40% as a criteria, in addition to signs and symptoms of HF.[13,16-18] On the other hand, some analyses either did not provide a distinction between HFrEF and HFpEF or included patients with HFrEF as well patients with HFpEF to compare the frequency of anemia and iron deficiency between the groups.[7,14] As data on the incidence of anemia and iron deficiency in HFpEF will be discussed in the next section, the information provided in this section covers the prevalence and incidence in HFrEF.

Because there is no consensus on the definition of anemia, different studies have reported different incidences for anemia. A commonly used definition is the one provided by World Health Organization (WHO), which defines anemia as hemoglobin (Hb) level of less than 13 g/dL in men and 12 g/dL in women.[19] Although this definition is commonly employed in the current practice, it is criticized for being outdated and being based on insufficient and low-quality data.[20] The analyses based on this WHO definition reported an anemia prevalence of 16%-49%.[15-18,15,21] Anemia prevalence varied between 10% to 17% in studies conducted with more conservative criteria (Hb ≤12 g/ dL for men, ≤11 g/dL for women).[11,16,22] Findings of a recent, multi-center, prospective observational study, which was conducted in Europe and included mainly HFrEF patients, has reported the prevalence of anemia as 28%.[7] The incidence of new-onset anemia in HF patients without previous anemia was 9.6% in SOLVD (Studies on Left Ventricular Dysfunction), 14.2% in COMET (Carvedilol or Metoprolol European Trial) and 16.9% in Val-HEFT (Valsartan in Heart Failure Trial).[2] Because all of these studies used hemoglobin criteria to define anemia, the proportion of anemias resulting from a true reduction in erythrocyte mass remains unclear. A study reported that dilution caused by fluid overload may be responsible for up to 46% of anemias, even in HF patients without clinical fluid overload.[12] Therefore, it should be noted that the figures on the prevalence and incidence of anemia may be influenced by additional factors such as decompensation status as well as the definition of anemia.

Most of the studies reported a higher prevalence of anemia among patients with iron deficiency compared to those with normal iron levels. Klip et al. reported the prevalence of iron deficiency as 35% in anemic patients versus only 22% in patients without anemia ($p<0.001$).[7] A study conducted in 2010 showed the

incidence of iron deficiency as 57% among anemic patients compared to an incidence of only 32% among non-anemic subjects.[4] As discussed below, the differences in definition had a major effect on different results regarding to the incidence of iron deficiency among anemic HF patients. For instance, incidence of iron deficiency was 78% in a study where iron deficiency was defined only on the basis of TSAT, while this incidence was as low as 20% when serum ferritin level was also included in the criteria in addition to TSAT.[23]

Investigations conducted only using peripheral blood samples may not adequately reflect the incidence of iron deficiency. An elegant study conducted by Nanas et al. showed that iron deficiency in bone marrow was present in 73% of the patients in HFrEF but without iron deficiency in peripheral blood samples.[24] While this study had suggested a much higher incidence for iron deficiency in HF patients compared to previous reports, the fact that anemia is normocytic even in patients with iron deficiency highlights the notion that iron deficiency is not the only etiological factor.[2,15] An analysis investigating the different etiological factors of anemia in HF patients failed to find a relevant factor in 57% of the 148 patients and these patients were classified as anemia of chronic disease based on laboratory findings.[25] However, iron deficiency was diagnosed using peripheral blood samples in this latter analysis. The fact that the chronic inflammation caused by HF leads to functional iron deficiency suggests that majority of these patients may in fact have multi-factorial anemia.

Iron deficiency should be considered as a comorbidity alone, even if it does not lead to anemia. As is the case with HF and anemia, the frequency of iron deficiency also depends on the definition. Studies based solely on "absolute" iron deficiency found the frequency of iron deficiency as 6%-21% in HF.[26]However, the cut-off value of ferritin to define iron deficiency used in these studies was 30 mg/dL, which was inappropriate for the diagnosis of iron deficiency in patients with chronic inflammatory conditions.[27]

Increased levels of IL-6 and other inflammatory cytokines interfere with iron absorption and transport of the readily available iron to the bone marrow, resulting in absolute as well as functional iron deficiency in HF.[28] A definition including both the absolute and functional components of iron deficiency would be serum ferritin ≤100 μg/L or serum ferritin level 100–299 μg/L with serum TSAT ≤20%. This definition was used in randomized controlled trials such as FAIR-HF (Ferinject Assessment in Patients With IRon Deficiency and Chronic Heart Failure) and CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure).[29,30] These studies have demonstrated the benefit of intravenous iron therapy in patients with absolute or functional iron deficiency.[29,30] Therefore, the functional form should also be taken into account when reporting the frequency of iron deficiency.

A large-scale prevalence study conducted using the aforementioned definitions reported the frequency of iron deficiency as 37% while another study found a rate of 50%.[7,12] In other words, when functional iron deficiency is included in the estimation, iron deficiency is seen in approximately 1/3 to 1/2 of all HF patients.

Studies on the prevalence of anemia and iron deficiency in heart failure are summarized in Table 3.

3.2 Do iron deficiency and anemia occur in heart failure with preserved ejection fraction?

Patients classified as heart failure with preserved ejection fraction (HFpEF) are older and have more comorbidities than those with HFrEF. Because both of these conditions increase the prevalence of anemia, one may expect anemia to be more common in HFpEF compared to HFrEF. However, a limited number of comparative studies did not found substantial difference between these two patients groups in terms of anemia frequency. A retrospective analysis of the CHARM (The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) studies which included both HFpEF and HFrEF patients, anemia was somewhat more common with HFpEF compared to HFrEF; however, the difference was not significant (27% vs 25%).[14] The analysis also showed that mean EF was higher in patients with anemia versus non-anemic patients (39 vs 38%, p=0.049) and EF was a standalone predictor of anemia.[14] The analysis conducted with the more recent data from SENIORS (The Study of the Effects of Nebivolol Intervention on OUtcomes and Rehospitalization in Seniors with Heart Failure) showed no difference between patients with EF <35% and >35% in terms of anemia prevalence (19.0% vs 18.7%, p=0.87).[31]

Table 3. Studies on the prevalence and incidence of anemia and iron deficiency in patients with chronic heart failure

Study subject	Frequency	Notes	References
Anemia prevalence in HF patients	11%–49%	Closely linked with the definition of anemia	11,13,15-17, 21,22
Anemia incidence in non-anemic HF patients	9.6%–16.9%	Data obtained from randomized controlled trials	2
Prevalence of "absolute" iron deficiency in HF patients	6%–21%	Considered only iron, ferritin or transferrin saturation	26
Prevalence of absolute or functional iron deficiency in HF patients	37%–50%	Ferritin <100 μg/L or Ferritin 100-299 μg/L with TSAT ≤20%	4,7
Prevalence of iron deficiency in anemic HF patients	20%–73%	The highest rate was reported in patients for whom iron reservoirs were evaluated with bone marrow biopsy	4,7,23,24
Prevalence of iron deficiency in non-anemic HF patients	22%–32%	Ferritin <100 μg/L or Ferritin 100-299 μg/L with TSAT ≤20%	4,7

HF: Chronic heart failure; TSAT: Transferrin saturation.

Both studies used the WHO criteria to define anemia.

On the other hand, both analyses employed data from randomized clinical trials. Observational studies including real-life data have indicated that anemia prevalence may be higher in HFpEF patients. Two small studies investigating the prevalence of anemia reported a prevalence of 45%-55%.[32,33] A study conducted in Olmsted region found a higher anemia prevalence (58%) among HFpEF patients in the prospective arm while anemia prevalence was also high (48%) in the HFrEF group.[34] An analysis on the data obtained from the prospective and observational ARIC (Atherosclerosis Risk in Communities) study showed a higher anemia prevalence in HFpEF patients compared to HFrEF among subjects with acute decompensation (71.2% vs 69.5%); however, the total anemia prevalence was considerably higher (70%) compared to other HF studies.[35] In a sub-analysis of OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure), which was an observational registry study in hospitalized patients, mean Hb was significantly lower among HFrEF patients compared to HFpEF.[36]The high prevalence of anemia observed in this study could be secondary to the presence of additional risk factors for anemia in decompensated patients.

In conclusion, the frequency of anemia in HFpEF patients is at least as high as that in HFrEF patients and population-based studies indicate that anemia prevalence may be even higher than HFrEF. Taking into account the other studies except the ARIC analysis which included decompensated patients, one may conclude that anemia prevalence ranges from 18.7% to 58% among HFpEF patients.

Majority of the studies on iron deficiency either included only HFrEF patients or all HF patients were included in the analyses without distinguishing HFpEF/HFrEF. Therefore, there is insufficient data on the prevalence of iron deficiency in HFpEF. In two studies with considerably small sample sizesand included only HFpEF patients, iron deficiency prevalence was found to be 57% and 70%. One of these studies excluded anemic patients while the latter included both anemic and non-anemic patients.[37,38] In an analysis of approximately 1500 patients including HFpEF as well as HFrEF cases, frequency of iron deficiency was reported to be 50%; however, this study did not provide the frequency of iron deficiency for each group.[7] While the currently available data suggest that iron deficiency prevalence is similar or higher in HFrEF patients compared to HFpEF, further studies are warranted to identify the prevalence more accurately.

Information regarding the studies on iron deficiency and anemia prevalence in HFpEF patients is summarized in Table 4.

Table 4. Studies on the prevalence of anemia and iron deficiency in patients with heart failure and preserved ejection fraction

Study subject	Frequency	Notes	Source
Data on anemia prevalence obtained from RCTs on HFpEF			
CHARM	27%	Higher anemia prevalence in HFpEF compared to HFrEF	14
SENIORS	18.7%	No difference versus HFrEF	31
Data from retrospective analyses or observational registries on HFpEF			
Brucks et al.	45%		32
Tehrani et al.	55%		33
Dunlay et al.	58%	Significantly higher (48%) compared to HFrEF	34
Caughey et al.	71.2%	Included acute decompensated patients	35
Iron deficiency prevalence in HFpEF patients			
Kasner et al.	57%	Included 26 HFpEF patients	37
Nuñes et al.	70%	Included 40 HFpEF patients	38

HFpEF: Heart failure with preserved ejection fraction; RCT: Randomized controlled trial; CHARM: The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; SENIORS: The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure.

3.3 What is the prevalence of iron deficiency and anemia in patients with acute heart failure?

Before discussing the prevalence in patients with acute heart failure (AHF), it should be noted that the anemia in some patients may not be true anemia, but may rather develop secondary to decompensation. As mentioned previously under a previous title, in 37 anemic patients with HF assessed for transplantation who had no clinical fluid overload, normal red blood cell mass and presence of "pseudoanemia" secondary to plasma expansion were found in 46%.[2] Similarly, a study by Abramov et al. showed that all patients with HFrEF had plasma volume expansion and only 57% of them had true red blood cell deficiency. Interestingly, plasma expansion was responsible for only a minority (12%) of anemias in patients with HFpEF in this study, i.e. the "true" prevalence of anemia in HFpEF may be higher than HFrEF.[39] Since plasma volume expansion may be expected to be higher in patients with decompensated heart failure requiring hospitalization, prevalence of anemia for AHF in observational studies is generally higher from that in chronic HF. Anemia is of prognostic importance in these patients regardless of an association with pseudoanemia; however, whether anemia requires specific therapy in these patients remains unclear.[11]

In a registry study of 1960 patients hospitalized for acute heart failure, prevalence of anemia was found to be 57% using WHO criteria.[40] In a sub-analysis of the OPTIMIZE-HF registry, Hb was ≤12.1 g/dL in 51.2% of the patients.[41] Also in the ADHERE study that evaluated data of more than 100,000 patients, prevalence of anemia was found to be 53%.[42] Contrary to other studies, a prevalence of 14.7% was reported in EHFS-II (Euro Heart Failure Survey II) registry in which frequency of anemia was higher in patients with decompensated chronic HF compared to those with de novo AHF (16.8%–11.3%, $p<0.001$).[43] Data from the observational TAK-TIK registry study that included 558 patients from Turkey reported mean Hb value as 12.4±2.1 g/dL in patients hospitalized for AHF.[44] No secondary analysis was performed for the presence of anemia in this study. However, a mean Hb value of 12.4 g/dL suggests that the prevalence might be close to 50%.[44] Analysis of the previously mentioned ARIC study revealed anemia prevalence as 70% in patients with AHF, and the

prevalence was found to be high both in HFrEF and HFpEF groups.[35] In summary, with the exception of EHFS-II registry, prevalence of anemia was found to be between 50-70% in majority of the studies, indicating a higher prevalence in AHF compared to chronic HF.

As indicated by the EHFS-II data, prevalence of anemia may be lower in patients with de novo AHF in whom the degree of plasma volume expansion is currently mild.[43] Studies investigating the prevalence of anemia in AHF are shown in Figure 1.

While it has been shown that treatment of iron deficiency with IV iron preparations reduces the combined endpoint of mortality and hospitalization in patients with chronic HF, large studies have recently evaluated the frequency of iron deficiency in AHF. In a study by Rovellini et al. in 2012 involving 200 patients hospitalized for AHF, the incidence of anemia thought to be associated with absolute iron deficiency was 6.9%. However, serum iron levels were low and TSAT was high in patients with both microcytic and normocytic anemia.[45]

In another study by Jankowska et al. in which iron deficiency was defined by low hepcidin and high soluble transferrin receptor concentration, the prevalence of iron deficiency was reported to be 37%.[46] In this study, it was particularly meaningful that iron deficiency was seen in one third of the patients

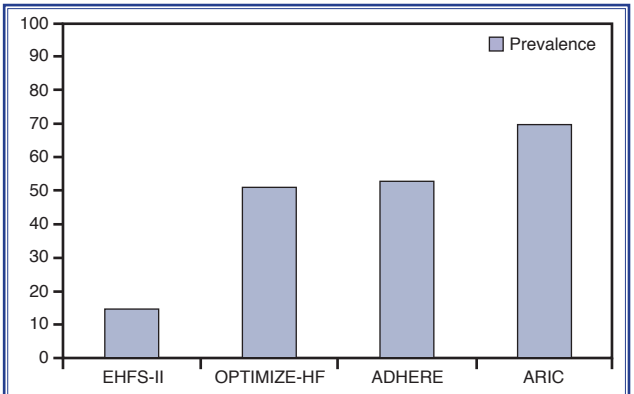


Figure 1. Studies investigating the prevalence of anemia in patients with acute heart failure. Values found for anemia prevalence in patients with acute heart failure in various observational registry studies. EHFS-II, Euro Heart Failure Survey II;[43] OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure;[41] ADHERE, Acute Decompensated Heart Failure National Registry;[42] ARIC, Atherosclerosis Risk in Communities.[35]

despite the different definition of iron deficiency as it remains unknown whether the standard definition used in FAIR-HF and CONFIRM-HF studies applies to AHF patients.[28,29,46–48] Iron deficiency prevalence was 70% and 74% respectively in two studies, one of which defined iron deficiency as serum ferritin level under <100 μg/L and the other defined it as serum ferritin level between 100–299 μg/L and serum transferrin ≤20%. Prevalence of absolute iron deficiency, on the other hand, is lower (48.2%).[49,50] As previously mentioned it is still discussed whether it is appropriate to use these criteria in AHF patients or whether they are related to prognosis.[51] As serum hepcidin/soluble transferrin receptor or absolute iron deficiency may be closely related to prognosis in AHF patients,[46,50] 37–49% of the AHF patients seem to have iron deficiency (approximately 1/3 to 1/2 of patients).

4.0 PROGNOSIS – Hakan Altay

4.1 Do iron deficiency and anemia influence the prognosis in heart failure?

Studies have shown that anemia is associated with the severity of HF and also predictive of high risk for both death and hospitalizations.[24,52,53] These studies show that anemia increases both short- and long-term mortality by 1.5–2 fold independentof the other clinical variables. Prognosis of HF gets worse especially when there is concomitant cardiorenal syndrome and anemia. In a study with HFrEF patients, Scrutinie et al. reported that HF, renal failure and anemia constitute a fatal combination which they called the “cardiorenal anemia syndrome”.[54]

The impact of anemia on the prognosis was also studied in well-known large HF trials. In the SOLVD study, a 10% increase in mortality was observed for each 1 g/dL decrease in hemoglobin levels.[55] In ValHEFT, it was demonstrated that the presence of anemia created a 20% increase in the risk of mortality and morbidity.[16] The same study showed that it was the change in hemoglobin levels over time that influenced prognosis rather than the overall hemoglobin values. In ValHEFT, new onset anemia was reported in 16.9% of the patients and there was a closer relationship between the change in hemoglobin levels over 12 months and late clinical endpoints compared to BNP, glomerular filtration rate (GFR) and even baseline hemoglobin level. It has also been shown

that improvement of anemia using intravenous iron preparations prevents adverse clinical events, reinforcing the importance of anemia in HF prognosis.[56]

Despite abundant evidence demonstrating the relationship between anemia and poor prognosis in HF, the mechanisms that describe this worsening of HF in anemic patients are not clearly understood. These mechanisms are both complicated and multifactorial. Factors that explain the poor prognostic relationship between anemia and HF include advanced age, higher prevalence of comorbidities and renal failure in particular, increased neurohormonal activation, chronic inflammation, and reduced free radical scavenging capacity. It is also possible that anemia is associated with poor prognosis due to severe underlying myocardial dysfunction.

Previously, the relationship between iron deficiency and HF was considered only in the context of anemia. However, after it was understood that a reduced hemoglobin level is the end result of a long process initiating with the depletion of ironstores, researchers have begun to focus on the relationship between iron deficiency without anemia and HF prognosis. Studies investigating the contribution of iron deficiency to HF prognosis have revealed conflicting results. Jankowska et al. showed in their study that reduced iron levels without anemia is a common finding in HF, and has negative effects on prognosis.[4] On the other hand, Parikh et al. showed that there is no association between iron deficiency and all-cause or cardiovascular mortality in patients with HF.[57] In this study, however, diagnosis of HF was established by asking patients and the severity of HF was not evaluated based on NYHA functional class and NT-proBNP levels. A large international study investigating patients with both HFrEF and HFpEF demonstrated that iron deficiency is common in HF (50%) and shows correlation with NYHA functional class as well as NT-proBNP levels both of which relates to severity of HF, and predicts mortality independent of other established factors (including anemia).[7] The prognostic importance of iron deficiency in HF has also been demonstrated in studies showing improved prognosis after treatment with IV iron preparationsin patients with heart failure accompanied by iron deficiency. Indeed, Anker et al. showed the favorable effect of IV iron treatment on prognosis in chronic HF both in patients with and without anemia.[29]

Studies showing the relationship between iron deficiency and prognosis in HF are summarized in Table 5. Although it is not clear whether anemia is the cause or the consequence of HF, it can clearly be stated that anemia has a strong relationship with the severity of HF and adverse events. In addition, it would not be erroneous to think that, iron deficiency is associated with high mortality and hospitalization as well as progression of HF regardless of the presence of anemia in HF and may be a more valuable prognostic tool than anemia in this context.

4.2 Do iron deficiency and anemia influence quality of life in heart failure?

Besides being associated with advanced chronic HF, iron deficiency also impairs the energy metabolism of both myocardium and skeletal muscles by reducing hemoglobin and decreasing oxygen transport. Furthermore, it may cause a reduction in myoglobin levels even in the absence of anemia, resulting in dysfunction of peripheral muscle tissues. Taking these effects into consideration, iron deficiency is thought to reduce exercise capacity, leading to decreased quality of life in HF regardless of presence or absence of anemia. Indeed, both CONFIRM-HF and FAIR-HF studies have shown an increase in 6-minute walking distance equivalent to that obtained with other medicines with proven benefits in addition to improvement in NYHA functional class and quality of life in patients with HF receiving IV iron treatment.[29,30] Jankowska et al. published a meta-analysis of studies comparing the effects of IV iron treatment in patients with HFrEF and found improved exercise time, NYHA functional class and quality of life with IV iron treatment.[58] In addition, they found that IV iron treatment provided these beneficial effects independent of anemia, emphasizing the importance of iron deficiency for exercise capacity and quality of life.

The hemoglobin in the blood plays an important role in supplying increased oxygen demand of both the myocardium and skeletal muscles during exercise. Since normal physiologic reserve is low in patients with HF, the decrease in hemoglobin level cannot be compensated, and results in reduced exercise capacity. As a matter of fact, studies confirmed a correlation between anemia and NYHA functional class in HF.[59]

Anemia is particularly observed in elderly HF patients with serious symptoms, low body mass index and cachexia, accompanied by chronic renal failure.

Table 5. Studies investigating the relationship of iron deficiency and anemia with prognosis in heart failure

Study	Year	Number of patients	Inclusion criteria	Primary endpoint	Results
Kosiborod et al.	2003	2281	Patients >65 years old hospitalized for HFz	Mortality Re-hospitalization	Anemia was found to be associated both with death and re-hospitalization
Mozaffarian et al. (PRAISE)	2003	1130	NYHA class III and IV, HFrEF (EF<30%)	Mortality	Anemia was found to be an independent risk factor for mortality. Each 1% decrease in Htc resulted in an 11% increase in death.
Ahmad et al. (SOLVD subgroup analysis)	1991	2569	Chronic HFrEF (EF<35%)	Survival according to GFR and Htc levels	Each 1 g/dL decrease in Hb was associated with a 10% increase in death.
Anand et al. (VaLHEFT subgroup analysis)	2005	5010	NYHA class II, III and IV, HFrEF (EF<40%)	Mortality and hospitalizations Hb change at 12 months and its impact on clinical events	Anemia was shown to increase the risk of mortality and morbidity by 20%. The relationship between mortality and new onset change in Hb at 12 months was shown to be even greater than the relationship with baseline anemia.
Jankowska et al.	2010	546	Mild-severe HFrEF (EF<35%)	All-cause death or heart transplantation	ID (not anemia) was shown to be associated with increased death or heart transplantation
Okonko et al.	2011	157	Patients with HFrEF (EF<35%)	Mortality Exercise capacity	ID was shown to be associated with exercise capacity and increased mortality regardless of Hb.
Parikh et al.	2011	574	Patients with self-reported HF	All-cause and CV mortality	No relationship between ID and mortality was reported.
Klip et al.	2013	1506	Patients with HFrEF (EF<45%) and HFpEF	Mortality NYHA functional class	ID was shown to be related with both NYHA class and NT-proBNP levels and with mortality regardless of anemia.

ID: Iron deficiency; HFrEF: Heart failure with reduced ejection fraction; EF: Ejection fraction; Hb: Hemoglobin; Htc: Hematocrit, CV: Cardiovascular; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; NYHA: New York Heart Association.

Therefore, the association between anemia and impaired quality of life is not unexpected in HF. Since there is a correlation between dilutional anemia and clinical congestion, anemia indicates symptomatic patients with worse outcomes.[12]

Anemia may lead to deterioration of symptoms and decreased functional capacity by enhancing direct neurohormonal activation and decreasing the bioavailability of nitric oxide (NO).[60] Studies investigating the influence of improving anemia by erythropoietic therapy on functional capacity and quality of life have reported conflicting results. Exercise capacity was found to increase with erythropoietin treatment

in patients with anemia and moderate to severe HF.[61] Another study reported that no increase was observed in functional capacity by treating anemia with darbepoetin alfa in 41 patients with anemia and HF.[62] In a recent study, darbepoetin provided no benefit on the clinical outcome in patients with mild to moderate anemia and systolic HF.[63] The STAMINA HeFT study conducted in patients with HFrEF and anemia evaluated the effect of darbepoetin on exercise duration, NYHA functional class and quality of life.[64] In this study, despite a significant increase in hemoglobin levels, darbepoetin did not provide any benefit on exercise duration, NYHA class and quality of life. The fact that no benefit was seen in terms of exercise and quality of life with erythropoietin despite the correction of anemia has been partially explained by the undesired effects of these drugs such as hypertension and thrombosis.

It is obvious that iron deficiency and anemia has an unfavorable impact on quality of life in HF. Results of the studies carried out to date indicate the need to target iron deficiency rather than hemoglobin levels in order to improve exercise capacity and quality of life. Indeed, European Heart Association 2016 Heart Failure guidelines recommend treatment with IV iron preparations with an indication level of class IIa in the presence of iron deficiency in order to improve exercise capacity and quality of life in symptomatic systolic HF.[6]

5.0 CLINICAL DIAGNOSIS

Mehmet Birhan Yılmaz

5.1 Which iron deficiency and anemia parameters should be routinely checked in patients with heart failure?

Also being indicated in various guidelines (Table 6), hemoglobin is recommended routinely in all patients newly diagnosed with HF according to the two most recent HF guidelines.[6,65] Anemia is an important parameter that determines the treatment modality in HF. Investigating iron deficiency parameters is also considered as a weak recommendation during the initial diagnosis of chronic HF. In addition, checking ferritin and transferrin saturation may be required rather than recommended in an HF patient with at least one hospitalization due to iron deficiency as iron deficiency is associated with poorer functional capacity and prognosis and may occur even in the absence of anemia.[66]

Complete blood count is among the routine tests for the diagnosis of acute and chronic HF. It may also be measured periodically during the follow-up. Ferritin and TSAT should be checked if hemoglobin levels are found to be lower than 15 g/dL at any time point in HFrEF patients with a certain extent of cardiac load and NYHA II-III symptoms (although inclusion criterion in CONFIRM-HF was <15 g/dL, benefit was more pronounced with <12 g/dL in the subgroup analysis). TSAT is a percentage value estimated by serum iron/total iron binding capacity. Total iron binding capacity

Table 6. Recommendations for anemia testing according to various guidelines

	Complete blood count	Recommendation level
2008 ESC HF	Complete blood count is a routine in the diagnostic investigation of HF	None
2012 ESC HF	Complete blood count is recommended in the diagnostic investigation of HF, differential diagnosis of acute HF, and determination of prognosis	Class 1C
	Ferritin and TIBC are recommended for treatment and determination of prognosis	Class 1 C
2016 ESC HF	Hemoglobin and WBC are recommended for eligibility for specific treatment in newly diagnosed HF and determination of modifiable causes, and complete blood count is recommended for the differential diagnosis of HF	Class 1C
	Ferritin and TSAT (TSAT=TIBC) are recommended for eligibility for specific treatment in newly diagnosed HF and determination of modifiable causes	Class 1C
2010 HFSA	Complete blood count is routinely recommended in the diagnostic investigation of chronic HF. Complete blood count is routine in acute HF.	Evidence level B (chronic)
2013 ACCF/AHA HF	Complete blood count is recommended in the diagnostic investigation of HF	Class 1C

TSAT: Transferrin saturation; TIBC: Total iron binding capacity; WBC: White blood cells.

is a measure of all proteins (majority of which is transferrin) that can bind to serum iron derived from the sum of unsaturated iron binding capacity and serum iron.

In patients diagnosed with anemia, evaluation of vitamin B12 and folate levels, occult blood test in the stool and peripheral smear are recommended as well as bone marrow biopsy if required for the diagnostic algorithms and etiologic differential diagnosis. At this point, particularly elevated RDW (red cell distribution width) levels and microcytic structure in peripheral smear are signals indicating iron deficiency.

5.2 Which criteria should the diagnosis be based on for iron deficiency and anemia in heart failure?

Definition of anemia according to World Health Organization is hemoglobin level below 13 g/dL for males over 15 years of age and below 12 g/dL for females over 15 years who are not pregnant. Anemia is a common condition among inpatients. Standard tests should be requested for the differential diagnosis of anemia for all patients with anemia.[67]

On the other hand, isolated iron deficiency does not mean anemia. Iron deficiency may occur in chronic inflammatory diseases in which only iron reservoirs are diminished or iron utilization is impaired, or in skeletal muscle dysfunction with or without anemia. Sole iron deficiency is associated with poor prognosis in HF even in the absence of anemia.[68]

The criteria recommended for the diagnosis of iron deficiency in the presence or absence of anemia according to 2016 European HF guidelines are presented in Table 7.[6]

5.3 What do absolute and functional iron deficiencies refer to? How is the diagnostic differentiationestablished?

Iron deficiency is considered in two types, namely absolute or functional. Absolute iron deficiency indicates diminished iron reservoirs in the body due to insufficient iron intake, impaired GIS absorption or chronic blood loss.[69] Functional iron deficiency indicates impaired iron absorption and utilization possibly due to increased hepcidin production and related inhibition of the iron carrier, ferroportin.[70]

Table 7. Criteria established for the diagnosis of iron deficiency in 2016 European heart failure guidelines

Absolute iron deficiency	Serum ferritin <100 μg/L
Functional iron deficiency	Serum ferritin 100-299 μg/L and transferrin saturation <20%

Diagnosis of iron deficiency is complicated in patients with heart failure. The standard threshold of iron deficiency defined as ferritin <30μg/L offers an acceptable sensitivity and specificity. However, this threshold does not apply to chronic diseases such as HF since ferritin is also an acute phase reactant.[66]

5.4 What is the role of hepcidin and bone marrow biopsy in diagnosis? Which patient, and when?

Dietary iron is reduced to Fe2+ by the duodenal cytochrome B in the lumen of duodenum and proximal jejunum. This is the region where iron enters enterocytes through the divalent metal transporter-1 (DMT-1).[71] Subsequently, the iron is released into the circulation by ferroportin located in the basal-lateral walls of enterocytes. In the circulation, iron is converted into Fe3+ by hephaestin and then binds to transferrin in the plasma.[71] Transferrin receptor-1 expressing cells uptake the transferrin-iron complex. Iron is stored in the liver, spleen and bone marrow as ferritin.

Hepcidin is a small peptide released by the liver to regulate iron homeostasis.[70] It binds to ferroportin and degrades this receptor, leading to the inhibition of iron absorption. As a result, iron accumulates in the enterocytes and is then eliminated by the shedding of intestinal cells.[46] This indicates that oral iron treatment is not expected to work in iron deficiency with high hepcidin levels. Likewise, neutral results were reported in the IRONOUT study which evaluated the effect of oral iron treatment in patients with HFrEF and was published last year.

Since ferroportin is also found in the macrophages of the reticulo-endothelial system, hepcidin traps iron within RES cells, thereby reducing utilizable iron.[46] Hepatic expression of hepcidin is decreased in iron deficiency and increased in iron overload or inflammatory diseases like heart failure.[66]

Bone marrow biopsy or aspiration is among the final steps in the differential diagnosis of anemia and provides insight about the production of blood cells. It also plays a role in the differential diagnosis of more serious diseases (e.g. leukemia). It is not required for the diagnosis of iron deficiency except for very serious conditions refractory to treatment or for the confirmation of response to treatment.[72]

6.0 TREATMENT OPTIONS AND CLINICAL BENEFIT – Nesligül Yıldırım

6.1 What are the treatment options for iron deficiency and anemia?

Oral iron salts such as ferrous sulfate are frequently used in patients with iron deficiency due to convenience and low cost; however, they are not the first choice in HF because of frequent gastrointestinal side effects, reduced gastrointestinal absorption due to food and drug interactions, further limitation of absorption because of the intestinal mucosal edema particularly in patients with HF and the slow onset of effect.[73,74] In a recent retrospective study, however, it was shown that oral iron treatment may enhance iron reservoirs similar to IV iron treatment in patients with HF.[75] The IRONOUT-HF study investigated the effects of oral iron polysaccharide treatment on exercise capacity compared to placebo in patients with functional iron deficiency in HF.[76] According to the results presented at AHA 2016, oral iron treatment has a mild effect on filling iron reservoirs and does not improve peak exercise capacity. It appears that questions on which HF patients may respond better to oral iron treatment and what sort of benefits oral treatment may offer will be further clarified in the future.

Intravenous iron treatment has drawn the attention of investigators owing to the absence of absorption problems and faster onset of effect compared to oral iron treatment. Iron sucrose, iron dextran, ferric gluconate and ferric carboxymaltose are frequently used IV iron preparations shown to exert various effects in experimental models. However, the clinical trial data comparing these agents are very limited.[73] Elevated markers of oxidative stress and inflammation, development of hypotension, and impaired renal and hepatic functions were observed in animals treated with iron dextran and ferric gluconate compared to those given ferric carboxymaltose and iron sucrose.[77,78] IV iron dextran is contraindicated since IV iron complexes containing dextran ligands may rarely have a risk of triggering anaphylactic reactions. Although rarely, iron preparations free of dextran also carry a risk of causing hypersensitivity reactions.[73]

Another important consideration regarding IV iron treatment is paying attention not to administer the treatment during an active infection as excessive iron increases the risk of infection by impairing the functions of T cells and neutrophils although iron is required for healthy immune response.[79] Jankowska et al. carried out a meta-analysis of five randomized controlled studies investigating the effects of IV iron treatment in patients with systolic heart failure and found that IV iron treatment improved NYHA class, increased the 6-minute walking distance and decreased the risk of the composite endpoint of all-cause death and cardiovascular hospitalization as well as the composite endpoint of cardiovascular death and hospitalization due to worsening of heart failure.[80]

Another treatment method for iron deficiency is to use erythropoiesis-stimulating agents. However, studies have reported that using erythropoiesis-stimulating agents alone offers no benefit in reducing mortality and hospitalization in patients with HF, and increases thromboembolic events. Therefore, they are not recommended for the treatment of iron deficiency in HF.[81]

Since blood transfusion has side effects including immunosuppression which increases the risk of infection, sensitization to HLA antigens and iron overload, it is considered in the acute treatment of serious anemia rather than the long-term treatment of chronic anemia.[82]

6.2 Does treatment for iron deficiency and anemia provide any clinical benefit?

Despite the advances in the treatment of heart failure, restriction of daily activities particularly due to dyspnea and fatigue impact life style and increase morbidity in many patients. Several mechanisms regardless of hemodynamic dysfunction are involved in the reduced exercise capacity in patients with HF. The leading mechanisms in this context are oxygen consumption and insufficient oxygen supply.[74,83]

Iron plays a role in oxygen uptake and transfer through hemoglobin, in oxygen storing through myoglobin, and in oxygen metabolism through oxidative enzymes and mitochondrial respiratory chain proteins, all of which contain iron in their structure, and also in erythropoiesis.[83]

The iron content of myocardium is shown to decrease in patients with HF, which is speculated to play a possible role in impaired systolic functions.[73,81]

Since energy production of myocardium and oxy-

gen utilization of skeletal muscles during exercise are impaired in the pathophysiology of HF, treating iron deficiency would be expected to contribute favorably to the treatment of heart failure.[73,81,84]

Several studies in recent years have shown that treating iron deficiency with IV iron preparations in patients with chronic HF may have positive effects on functional capacity and quality of life.[30,56,73,81,84] As a matter of fact, Jankowska et al. carried out a meta-analysis of five randomized controlled studies investigating the effects of IV iron treatment in patients with HFrEF and found that IV iron treatment improves NYHA class (–0.54 class, 95% CI –0.87 to –0.21, p=0.001), increases the 6-minute walking distance (+31 m, 95% CI 18–43, p<0.0001), and improves quality of life (Kansas City Cardiomyopathy Questionnaire (KCCQ) score: +5.5 points, 95% CI 2.8–8.3, p<0.0001; European Quality of Life–5 Dimensions (EQ-5D) score: +4.1 points, 95% CI 0.8–7.3, p=0.01; Minnesota Living With Heart Failure Questionnaire (MLHFQ) score: –19 points, 95% CI –23 to –16, p<0.0001; Patient Global Assessment (PGA): +0.70 points, 95% CI 0.31–1.09, p=0.004). Moreover, they observed these positive effects on exercise capacity, quality of life and symptoms in both anemic and non-anemic patients with iron deficiency.[58] The details of the studies included in the meta-analysis by Jankowska et al. are presented in Table 8.

6.3 Does treatment for iron deficiency and anemia affect mortality?

In several studies performed to date, presence of iron deficiency in patients with HF has been shown to be closely associated with mortality regardless of the seriousness of heart failure and the presence of anemia.[79]

However, answers are not equally clear regarding the effect of correcting iron deficiency on mortality. Among subjects with heart failure and anemia in the FAIR-HF study, no difference was detected between the group receiving IV iron treatment and the group

Table 8. Comparison of characteristics of the studies investigating the clinical effects of intravenous iron treatment

	Toblli et al. (n=40)	FERRIC-HF (n=35)	FAIR-HF (n=459)	IRON-HF (n=16)	CONFIRM-HF (n=301)
IV iron preparation	Iron sucrose	Iron sucrose	Ferric carboxymaltose	Iron sucrose	Ferric carboxymaltose
Administration	200 mg/week Treatment duration 5 weeks	-Correction phase: 200 mg/week (until ferritin >500 µg/L) -Maintenance phase: 200 mg every 4 weeks Total treatment duration 16 weeks	-Correction phase: 200 mg/week -Maintenance phase: 200 mg every 4 weeks Maximum treatment duration 24 weeks	200 mg/week Treatment duration 5 weeks	-Correction phase: 500-2000 mg -Maintenance phase: 500 mg Maximum treatment duration 36 weeks
Follow-up	5 months post-treatment	2 weeks post-treatment	Up to 24-26 weeks	Up to 3 months	Up to 52 weeks
NYHA class	Improvement	Improvement	Improvement	–	Improvement
6-minute walking distance	No appropriate data for meta-analysis	–	Increased	–	Increased
Quality of life	Improvement	Improvement	Improvement	–	Improvement
LVEF	Increased	No difference between groups	–	–	–
NTproBNP	Decreased	–	–	–	–

LVEF: Left ventricular ejection fraction; Hb: Hemoglobin; TSAT: Transferrin saturation; CrCl: Creatinine clearance; peak VO2: Peak O2 consumption; NYHA Class: New York Heart Association class; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Table 9. Comparison of characteristics of the studies included in the meta-analysis by Jankowska et al. evaluating the effects of intravenous iron treatment on mortality

	Toblli et al.	FERRIC-HF	FAIR-HF	IRON-HF	CONFIRM-HF
All-cause death	Data not included in meta-analysis	Data not included in meta-analysis	No difference between groups	Data not included in meta-analysis	No difference between groups
CV death	–	–	No difference between groups	–	No difference between groups
All-cause death CV hospitalization	–	–	No difference between groups	–	No differenceor between groups
CV death or hospitalization due to worsening HF	–	Data not included in meta-analysis	No difference between groups	–	Decreased in the group receiving intravenous iron treatment
HF hospitalization	Data not included in meta-analysis	Data not included in meta-analysis	No difference between groups	–	Decreased in the group intravenous iron treatment
First hospitalization due to any CV cause	–	–	Decreased in the group receiving intravenous iron treatment	–	–

LVEF: Left ventricular ejection fraction; Hb: Hemoglobin; TSAT: Transferrin saturation; CrCl: Creatinine clearance; peak VO2: Peak O2 consumption; CV: Cardiovascular; HF: Heart failure.

receiving placebo in terms of death due to cardiovascular causes, death due to worsening of HF, and hospitalization or death due to any cardiovascular cause while only the rate of first hospitalization due to any cardiovascular cause was found to be significantly lower in the group receiving IV iron treatment.[83] Similarly, no difference was found between the groups regarding death due to cardiovascular causes and death due to worsening of HF in the CONFIRM-HF study whereas hospitalizations due to worsening of HF were seen with a significantly lower rate in the group receiving IV iron treatment.[30] Currently, large studies evaluating the effect of IV iron treatment on mortality are limited to CONFIRM-HF and FAIR-HF. However, Jankowska et al. evaluated the data from 5 randomized controlled studies in this field by means of a meta-analysis and found that IV iron treatment decreased the risk of the composite endpoint of all-cause death or cardiovascular hospitalization (OR 0.44, 95% CI 0.30–0.64, p<0.0001) as well as the composite endpoint of cardiovascular death or hospitalization due to worsening of heart failure (OR 0.39, 95% CI 0.24–0.63, p=0.0001).[30,56,79,83–85] On the other hand, no effect was detected on all-cause mortality or cardiovascular mortality. Comparison of characteristics of the studies included in the meta-analysis by Jankowska et al. is presented in Table 9.

7.0 CLINICAL STUDIES AND GUIDELINE RECOMMENDATIONS ON TREATMENT

Ahmet Temizhan

7.1 Is treatment necessary in non-anemic iron deficiency?

Iron deficiency and anemia do not have the same meaning but refer to conditions with similar consequences. Iron deficiency has been found despite the absence of anemia in approximately 46% of the patients with low EF and stable HF.[7] The iron-containing oxygen transport proteins in red blood cells are one of the most important structures of hemoglobin, the levels of which determine the decision of anemia. These iron containing proteins play a very critical role

in vital cellular functions including oxygen storage (myoglobin) and energy production.

Similar to that seen in anemia, exercise capacity and maximal oxygen consumption decreases when iron deficiency develops in humans without any drop in hemoglobin values.[86,87] Iron deficiency is frequently seen in HF and it causes skeletal muscle dysfunction and abnormal energy metabolism without causing anemia as is the case in other chronic diseases,[69] resulting in increased symptoms as well as poor prognosis. Therefore, it would not be wrong to expect the treatment of iron deficiency to be independent from anemia since its negative effects also appear to be independent from anemia. Three studies supporting this expectation are FERRIC-HF (Ferric Iron Sucrose in Heart Failure),[84] FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure),[88] and CONFIRM-HF (Ferric CarboxymaltOse evaluation on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure).[30] Findings of these three studies are consistent with each other and show that, regardless of anemia, IV iron treatment is a safe treatment which increases exercise capacity (quantitatively with the 6-minute walking distance[30] and pVO2/kg[84]), relieves symptoms, improves NYHA functional class and quality of life with an onset of effect as rapid as within 1 month,[88] and reduces hospital admissions and worsening of HF over one year.[30] Therefore, these results indicate that treatment with IV iron should be considered in patients with a NYHA functional class of II-IV and HFrEF (left ventricular EF ≤45%) when serum ferritin level is <100 μg/L or serum ferritin level is 100-299 μg/L with TSAT <20%, even in the absence of anemia.

7.2 What are the key messages of large clinical studies on the treatment of iron deficiency and anemia?

Lack of efficacy with erythropoietin treatment in chronic HF patients with anemia has directed the approaches towards iron deficiency as the focus of new investigations. Important studies have been published regarding the efficacy of IV iron treatment in HF patients with or without anemia during the last decade. Among the studies discussed herein, those other than FAIR-HF[29] (number of patients >450) and CONFIRM-HF[30] (number of patients >300) have evaluated a limited number of subjects; however, their contribution in the context of methodology and results have been generally accepted. Detailed information about these studies is presented in Table 10 and 11.

Toblli JE et al.[56] started the journey basically from the frequent co-existence of iron deficiency anemia, chronic HF and chronic renal failure. They investigated the effects of IV iron treatment without erythropoietin on the problems caused by anemia in these patients. The study showed that hemoglobin, ferritin and TSAT values were increased with IV iron treatment. Furthermore, the most striking findings were, the improvements observed on left ventricular EF, NYHA functional class, exercise capacity, renal functions and quality of life. Interestingly, clinical improvement was associated with the improvement in iron parameters rather than the increase in hemoglobin levels. Although this study does not provide insight on the iron deficiency not accompanied by anemia, it is still considered an important study demonstrating that IV iron treatment is an important choice in patients with HF accompanied by chronic renal disease and anemia.

The FERRIC-HF study[84] showed that IV iron replacement increases exercise capacity and improves symptoms particularly in anemic HF patients with iron deficiency. The results were also not negative in patients without anemia. Despite not being statistically significant, a trend towards improvement was observed in these parameters. As seen in the study by Toblli et al.,[56] clinical improvement was associated with improved iron parameters and not with the increase in hemoglobin values. Despite the limited number of subjects, the evaluation of exercise capacity with a quantitative method such as pVO2/kg is among the properties that make FERRIC-HF a valuable study.

The FAIR-HF study has the highest number of subjects among the studies investigating IV iron replacement.[29] FAIR-HF revealed 4 key messages: 1- In case there is iron deficiency in symptomatic but stable patients with HF, IV replacement treatment with ferric carboxymaltose improves symptoms, increases physical performance and quality of life, regardless of the presence of anemia. This finding indicates that iron deficiency is a better treatment target than anemia. 2- Clinically beneficial effects occur within a short period, i.e. at 4 weeks of treatment. 3- Routinely investigating iron deficiency in symptomatic patients with HF may be an appropriate approach. 4- Results regarding clinical benefit are valid for patients with

Table 10. Design characteristics of important studies on intravenous iron treatment in chronic heart failure patients with iron deficiency

Study	Study design	IV iron preparation and dosage	N Treatment	N Placebo	Clinical inclusion criteria	Inclusion criteria based on iron status	Inclusion criteria based on Hb status (g/dL)	Treatment duration	Follow-up duration	Endpoint: events	Endpoint: parameters
Toblli 2007[56]	Double-blind randomized placebo controlled	ISC 1000 mg	20	20	LVEF≤35%, NYHA class II-III CrCl <90 mL/min	Ferritin <100 µg/L or TSAT <20%	M <12.5 F <11.5	5 weeks	5 months	All-cause death. Hospitalization due to HF	NYHA class MLHFQ score LVEF
FERRIC-HF 2008[84]	Double-blind randomized placebo controlled	ISC 1433 ± -365 mg	24	11	LVEF≤45%, NYHA class II-III Peak VO2 ≤18 mL/min/kg	Ferritin <100 µg/L (or 100-300 µg/L if TSAT <20%)	<12.5 (anemic group) 12.5-14.5 (non-anemic group)	16 weeks	2 weeks	All-cause death. All-cause death or hospitalization due to CV causes. Hospitalization due to HF	PGA NYHA class MLHFQ score LVEF
FAIR-HF 2009[29]	Double-blind randomized placebo controlled	FCM Mean 1850 mg	304	155	LVEF≤40%, NYHA class II LVEF≤45%, and NYHA class III*	Ferritin <100 µg/L (or 100-299 µg/L if TSAT <20%)	9.5-13.5	24 weeks	24-26 weeks	All-cause death. CV death, all-cause death or hospitalization due to CV causes. CV death or hospitalization due to worsening HF. Hospitalization due to HF	PGA NYHA class 6 minute walking distance, EQ-5D score, KCCQ score
IRON-HF 2013[85]	Double-blind randomized placebo controlled	ISC 1000 mg	10	6	LVEF≤40%, NYHA class II-IV	Ferritin <500 µg/L and TSAT <20%	≥9.0 - ≤12.0	5 weeks	3 months	All-cause death	–
CONFIRM-HF 2014[30]	Double-blind randomized placebo controlled	FCM Mean 1500 mg	150	151	LVEF≤45%, NYHA class II or III, BNP >100 pg/mL or NT-proBNP >400 mg/mL	Ferritin <100 µg/L (or 100-300 µg/L if TSAT <20%)	<15	36 weeks	52 weeks	All-cause death. CV death. All-cause death or hospitalization due to CV causes. CV death or hospitalization due to worsening HF. Hospitalization due to HF	PGA NYHA class 6 minute walking distance, EQ-5D score, KCCQ score

IV: Intravenous; Hb: Hemoglobin; LVEF: Left ventricular ejection fraction; NYHA Class: New York Heart Association class; CrCl: Creatinine clearance; M: Male; F: Female; ISC: Iron sucrose; FCM: Ferric carboxymaltose; TSAT: Transferrin saturation; PGA: Patient's global assessment; MLHFQ: Minnesota Living With Heart Failure Questionnaire; EQ-5D: European Quality of Life – 5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; HF: Heart failure; CV: Cardiovascular.

Table 11. Baseline characteristics of patients included in important studies on iron treatment in chronic heart failure patients with iron deficiency

Study	Baseline characteristics*									
	Age (y)	Male (%)	Ischemic HF (%)	NT-ProBNP (pg/mL)	LVEF (%)	NYHA sınıfı	Hb (g/dL)	Anemia (%)	Ferritin (μg/L)	TSAT
Toblli 2007[56]	76±7	VY	63	256±125	31±4	2.9	10.3±0.6	100	73±30	20±1
FERRIC-HF 20084	64±14	28	74	VY	30±7	2.5	12.6±1.2	50	62±37	20±8
FAIR-HF 2009[29]	68±10	54	80	VY	32±6	2.8	11.9±1.3	65	53±55	18±13
IRON-HF 2013[85]	67±8	33	22	VY	25±9	VY	11.2±0.6	100	185±146	19±10
CONFIRM-HF 2014[30]	69±10	47	83	2511±5006	37±8	2.5	12.4±1.41	53	57±48	20±18

*Values in the treatment arm. Hb: Hemoglobin; LVEF: Left ventricular ejection fraction; HF: Heart failure; NYHA: New York Heart Association; TSAT: Transferrin saturation; ND: No data.

a hemoglobin level <13.5 g/dL. This study provided no information regarding IV iron replacement for patients with hemoglobin levels higher than this value.

The most important characteristic of the IRON-HF study[85] is that it compared the efficacy of IV and oral iron treatment in chronic HF patients with anemia associated with iron deficiency. Despite the recovery of anemia in both replacement approaches, functional capacity was increased only in patients receiving IV iron treatment. The finding of no improvement in patients receiving oral therapy supports that the oral iron replacement approach frequently prescribed in outpatient follow-up is in fact not a favorable option.

CONFIRM-HF is the most recent and one of the most important studies guiding treatment approaches for iron deficiency in European Heart Failure guidelines together with FAIR-HF.[30] The characteristics of CONFIRM-HF which distinguish this study from others may be summarized as follows: 1- A simpler and more applicable iron replacement protocol has been developed using ferric carboxymaltose, 2- It provided a long-term evaluation for both the primary endpoint, i.e. 6 minute walking distance over 24 weeks and the second endpoints, i.e. NYHA functional class, patient's global assessment and quality of life questionnaires over 52 weeks, and 3- Clinically solid endpoints including mortality and morbidity in the context of secondary endpoints were also analyzed:

- All hospitalizations, all hospitalizations due to cardiovascular causes, hospitalization due to worsening of heart failure
- Time to first hospitalization due to any cause, time to first hospitalization due to any cardiovascular cause, and time to first hospitalization due to worsening of heart failure
- Time to all-cause death, time to any cardiovascular death, and time to death resulting from worsening of heart failure

At the end of the study, significant improvements were achieved in symptoms, functional capacity, quality of life and hospitalizations due to worsening of HF for over one year in symptomatic HF patients with iron deficiency receiving IV ferric carboxymaltose treatment for 36 weeks. CONFIRM-HF provided hints indicating that iron treatment may reduce clinical morbidity/mortality outcomes even if the findings are not too powerful owing to the fact that this study was not primarily designed for endpoints related to mortality and morbidity.

7.3 What do heart failure guidelines recommend regarding the treatment of iron deficiency and anemia?

The recommendation that takes into consideration the most detailed and recent studies has been included in 2016 European Heart Failure guidelines. Unlike the

previous European guidelines and other guidelines, the topic was discussed as iron deficiency instead of anemia.[6] The recommendation is quite clear and iron treatment is recommended regardless from anemia:

- Treatment with IV ferric carboxymaltose is recommended in order to improve symptoms of HF and to improve exercise capacity and quality of life in the presence of iron deficiency (serum ferritin level <100 μg/L, or serum ferritin level 100-299 μg/L with TSAT <20%) in patients with symptomatic HFrEF. (Class IIa, evidence level A).

8.0 INTRAVENOUS IRON THERAPY

Dilek Ural

8.1 How effective are intravenous iron preparations in iron deficiency associated with heart failure?

The most important effect of intravenous iron preparations in HF patients with iron deficiency is related to functional capacity and improvement of NYHA class, 6 minute walk test and quality of life regardless of anemia.[29] The improvement in functional capacity becomes noticeable after the fourth week and continues for a relatively long period until week 52.[30] In a meta-analysis of five major studies investigating IV iron treatment, Qian et al.[81] found that hospitalization rates due to HF decreases significantly in the active treatment group (odds ratio [OR] 0.28; 95% confidence interval [CI], 0.16–0.49; p<0.001). This finding may be important not only for the quality of life of HF patients but also for healthcare costs. As a matter of fact, studies from various countries indicate that IV iron treatment is a cost-effective treatment option for patients with HF.[89,90]

The effect of iron replacement on mortality has not been proven in the currently available studies. Since this may be related to the limited number of subjects included in the studies and short period of follow-up, the effect on major clinical endpoints, mortality in particular, has been investigated in various meta-analyses. Clevenger et al.[91] investigated the effect of iron replacement on 1-year mortality in a meta-analysis of 64 controlled studies conducted in 9004 subjects including patients with HF, and no difference was detected between the control and the active treatment groups. In another meta-analysis of five randomized controlled studies evaluating only patients with HFrEF, the composite endpoint of all-cause death and cardiovascular hospitalization was reduced by 56% among subjects receiving IV iron treatment (n=509) compared to the control group (n=342) (OR 0.44, 95% CI 0.30–0.64, p<0.0001).[58] In evaluation of individual components of the composite endpoint, no effect was observed on all-cause or cardiovascular death. On the other hand, the number of reported deaths were only 20 (4%) in the active treatment group and 19 (6%) in the control group, with a relatively short duration of follow-up.

The effects of IV iron treatment other than the effects on major clinical endpoints have been assessedin various studies. In the FAIR-HF study investigating renal functions, estimated glomerular filtration rate (eGFR) at 24 weeks was increased by 2.98±1.44 mL/min/1.73 m^2 in patients treated with IV ferric carboxymaltose compared to placebo (p=0.039), and this effect remained the same between patients with baseline eGFR values below or higher than 60mL/min/1.73 m^2.[92] The effect on NT-proBNP and C-reactive protein was investigated in the study by Toblli et al.[56] in which IV iron sucrose was used in patients with renal failure (creatinine clearance <90 mL/min) and significant reductions were observed in both markers at six months compared to placebo. In another study by the same team which investigated echocardiographic changes, significant decreases were observed in left ventricular systolic and diastolic diameters with a 6.6% absolute increase in ejection fraction in the active treatment group.[93] The increase in ejection fraction has also been assessed in other studies which reported a2% increase in 12 weeks as in the study by Gaber et al.[94] and 8% in 6 weeks in the study by Núñez et al.[95]

The effects of IV iron preparations on clinical endpoints and laboratory and echocardiographic variables in current studies are summarized in Table 12.

8.2 Can we use any intravenous iron preparation in iron deficiency? Is B12/folate supplement necessary?

Various IV iron preparations are available for the treatment of iron deficiency including ferric carboxymaltose, ferric-hydroxide sucrose, ferric gluconate, ferumoxytol, iron isomaltoside and ferric-hydroxide dextran. Two IV iron preparations have mainly been investigated in studies on the treatment of iron deficiency in patients with HF: 1) ferric-hydroxide sucrose (alone or in combination with erythropoiesis-stimula-

Table 12. The effects of intravenous iron preparations on clinical endpoints and laboratory tests

Clinical endpoint		
Mortality	All-cause death	Death was reported in 39 cases (4% in the treatment group vs 6% in the control group) in meta-analyses, and the OR for all-cause death was 0.81, 95% CI 0.42-1.57.[81]
Hospitalization	Hospitalization due to worsening HF	Hospitalization due to HF was significantly reduced (OR 0.28; 95% CI 0.16-0.49; p<0.001).[81]
	Composite endpoint of death and hospitalization due to HF	Reduced by 53% with iron replacement compared to placebo (OR 0.47; 95% CI 0.29-0.76; p=0.002).[81]
Functional capacity	NYHA class	Mean class decreased by 0.54-1.2.[58,96]
	6-minute walktest	At 24 weeks in the CONFIRM-HF study, it was increased by 18±8 m in the FCM group, and decreased by 16±8 m in the placebo group (p=0.002).[30] The increase in walking distance is ~31 m for the active treatment group in meta-analyses.[58]
	Patient's global assessment	Significant improvement was observed in patient's self-assessment.
Quality of life	KCCQ score	Increased by ~5.5 points in the active treatment group (95% CI 2.8-8.3, p<0.0001)[58]
	Other scorings	European Quality of Life-5 dimensional (EQ-5D) score and Minnesota Heart Failure and Life Questionnaire score were improved by +4.1 points and -19 points, respectively.[58]
Endpoints in laboratory investigations		
NT-proBNP		Decreased by 389 pg/mL in the active treatment group compared to the control group[93]
C-reactive protein		Decreased by 5.4 mg/L in the active treatment group compared to the control group[93]
Hematologic variables	Hemoglobin	Increased by 2.0-5.9 g/dL compared to the control group after approximately 6 months of follow-up.
	Ferritin	Increased by 145-265 μg/L compared to the control group after approximately 6 months of follow-up.
	Transferrin saturation	Increased by 6.6-8.9% compared to the control group after approximately 6 months of follow-up.
Renal functions	eGFR	Increased in the active treatment group compared to placebo (3-12 mL/min)[96]
Echocardiographic findings	Ejection fraction	Increased by 5.0% (95% CI 0.13-9.80) on average.[96]

FCM: Ferric carboxymaltose; CI: Confidence interval; KCCQ: Kansas City Cardiomyopathy Questionnaire; HF: Heart failure; OR: Odds ratio; eGFR: Estimated glomerular filtration rate.

ting agents), and 2) ferric carboxymaltose. Iron sucrose is approved for the treatment of chronic renal failure and iron deficiency, and should be given by slow IV injection over 30-60 minutes up to a maximum dose of 200 mg, requiring a total of ~5–7 injections. Since it is a safe treatment, no test dose against allergic reactions is required before administration. Iron sucrose has been tested in FERRIC-HF and IRON-HF studies, and improved functional capacity regardless of the presence of anemia (Table 13).[84,85]

However, the number of subjects included in these two studies were relatively limited (35 and 18, respectively) and the follow-up period was short (16 weeks and 3 months, respectively).

Table 13. Randomized controlled studies with ferric-hydroxide sucrose and ferric carboxymaltose in patients with heart failure

	Studies in patients with HF	Administration	Outcome
Ferric (iron III) hydroxide sucrose	FERRIC-HF[84] (n=35; follow-up 16 weeks)	Weekly 200 mg, until ferritin >500 μg/L, followed by monthly	Ferritin, VO2, treadmill exercise duration, NYHA functional class and patient's global assessment were 200 mg improved in patients given active treatment compared to the control groups and no difference was seen in adverse events. Favorable effects were more markedin patients with anemia.
	IRON-HF (n=18; follow-up 3 months)[85]	IV 200 mg once a week for 5 weeks	Peak oxygen utilization (VO2) increased in the parenteral treatment group compared to the oral treatment and control groups.
Ferric carboxymaltose	FAIR-HF (n=459; follow-up 24 weeks)[29]	200 mg IV, once a week	Improvements were seen in NYHA functional class, 6-minute walktest and quality of life assessments regardless of the presence of anemia in the active treatment group compared to placebo. Death rates, undesired events and serious adverse events were similar in both study groups.
	CONFIRM-HF (n=304 patients; 52 weeks)[30]	Based on specific dose scheme	6-minute walking distance, NYHA functional class, patient's global assessment, quality of life, fatigue score and rate of hospitalization due to worsening heart failure were reduced in the active treatment group regardless of the presence of anemia. There was no difference in terms of death and adverse events compared to placebo.

Ferric carboxymaltose is a polynuclear iron (III)-hydroxide carbohydrate complex designed to resemble physiologic ferritin. Advantages of this complex include thesuitability to be administered in higher doses with a single injection, ashorter time required for the infusion and decreased numberof infusions to compensate the iron gap. In addition, the initial administration does not require a test dose for allergic reactions as it is free of dextran.

Evidence indicating the favorable effects of IV iron treatment in patients with HF are predominantly obtained from studies with ferric carboxymaltose (FAIR-HF[29] and CONFIRM-HF[92]). Among these preparations, ESC 2016 Heart Failure Guidelines recommended only ferric carboxymaltose recommended as a class I indication and level of evidence A, to relieve the symptoms of HF and improve exercise capacity and quality of life in symptomatic patients with HFrEF diagnosed with iron deficiency (serum ferritin <100 μg/L or serum ferritin 100–299 μg/L and TSAT <20%).[6]

Vitamin B12/folate deficiency should be sought as a potential cause of anemia in HF. In currently available studies, however, anemia resulting from B12/folate deficiency has been rarely observed in the HF group.[97]

Besides, there is no evidence indicating reduced cardiovascular events with replacement.[98] In general practice, iron depots are rapidly consumed following accelerated erythropoiesis, resulting in iron deficiency in patients treated with supplementary B12 and folate. Therefore, patients receiving supplementary B12 and folate may be followed up for iron deficiency, and

iron supplement may be employed if necessary.

Blood transfusion may cause volume overload in patients with HF and therefore, it is not recommended with the exception of serious anemia (hemoglobin <7 g/dL).

8.3 How and for how long should intravenous iron therapy be administered? What should be the target for hemoglobin and iron levels?

The total iron dose required for iron replacement is calculated with the Ganzoni formula:[99]

Total iron dose to be administered (mg) = Weight (kg) x (Normal hemoglobin – patient's hemoglobin) x 2.4 + 500

While the normal hemoglobin value in the formula may be adopted as 12 g/dL for women and 13 g/dL for men, a standard level of 15 g/dL for both genders may also be applied. Depending on the calculated difference, the deficiency may be replaced with a single injection, or may require multiple doses. The preparation recommended in ESC 2016 Heart Failure guidelines is ferric carboxymaltose, which may be administered by one of the two following methods:

1) Intravenous bolus injection – The maximum dose that can be administered as a single bolus injection is 200 mg, and no more than 3 injections are allowed per week. The bolus injection method was preferred in the FAIR-HF study where weekly ferric carboxymaltose equivalent to 200 mg iron was administered during the treatment period until the calculated iron deficiency was replaced. During the maintenance period, the dose was repeated every four weeks (often starting at week 8 or 12) based on the control values. Treatment was interrupted when control ferritin level was>800 µg/L or ferritinis between 500–800 µg/L and TSAT >50% or hemoglobin >16 g/dL; and treatment was resumed for ferritin level <400 µg/L, TSAT <45% and hemoglobin level <16 g/L.

2) Intravenous infusion – The maximum dose that can be administered as a single intravenous infusion is no more than 1000 mg. A single dose should not exceed 15 mg/kg or the total calculated dose. The recommended administration is dilution in 50 mL or 100 mL 0.9% NaCl for 100-200 mg and 200-500 mg, respectively, for an infusion over at least 6 minutes, or a 15-minute infusion after dilution in 250 mL 0.9% NaCl if the iron dose to be administered is 500-1000 mg.

Iron deficiency was calculated as per the Ganzoni formula also in the CONFIRM-HF study, with an attempt to simplify the treatment protocol by employing a table (Table 14).[100] The initial dose was a single dose of 500-1000 mg followed by 500 mg iron maintenance every 6 weeks based on ferritin and TSAT. Although a high dose was used, the undiluted ferric carboxymaltose was administered as IV bolus injections over at least one minute.

Overall, both studies used an average of ~1000 mg (200–1900 mg) iron during the treatment period and 875 mg (200–1000 mg) through the maintenance period; and while the total median dose was 2000 mg in FAIR-HF (dose range 200–2400 mg), the median dose over 52 weeks was 1500 mg (dose range 500–3500 mg) in CONFIRM-HF. In more than 75% of the CONFIRM-HF patients, a maximum of two doses was sufficient to correct and maintain iron parameters. On the other hand, the median number of injections was 6 in the FAIR-HF study. While different protocols are evaluated for the route of administration with attempts to accelerate the process and decrease the number of injections, one may conclude that currently the most practical method is the protocol employed in CONFIRM-HF.

Table 14. Treatment schedule of the CONFIRM-HF study

Treatment period					
Patient's body weight	<70 kg		≥70 kg		All
Hemoglobin	<10 g/dL	≥10 g/dL*	<10 g/dL	≥10 g/dL*	>14 ve <15 g/dL
Week 0	1000 mg	1000 mg	1000 mg	1000 mg	500 mg
Week 6	500 mg	None	1000 mg	500 mg	None
Maintenance period					
Week 12, 24, 36	500 mg (if serum ferritin <100 µg/L or serum ferritin 100–300 µg/L and TSAT <20%)				

Hb: Hemoglobin; TSAT: Transferrin saturation; *Hemoglobin ≥10 g/dL and ≤14 g/dL.

Currently, there is no exact consensus regarding the ideal treatment target. Anemia is defined as hemoglobin levels below 12 g/dL for women and 13 g/dL for men as per World Health Organization guidelines on the diagnosis and treatment of anemia.

In the FAIR-HF study, target hemoglobin level was calculated as 15 g/dL utilizing the Ganzoni formula, and the hemoglobin value achieved at the end of treatment was 13 g/dL. However, there is no target hemoglobin level specified for patients with HF, and high levels of hemoglobin are even considered as potentially hazardous. Therefore, it appears reasonable to maintain hemoglobin levels ~12 g/dL based on the currently available data. Similarly, there is no clear target value for iron levels, either.[101] The target ferritin level was >500 ng/mL (value achieved at the end of treatment: 312 µg/L) in the FAIR-HF study and >100 µg/L or TSAT >20% if ferritin was 100–300 µg/L in the CONFIRM-HF study. Different targets are selected in different studies. Taking the follow-up period and patient's comfort into account, the targets in CONFIRM-HF appear to be more applicable. Regardless of the target specified, maintenance of these values should be checked by repeated tests every 3 months.

8.4 What are the possible side effects of intravenous iron administration? Can we administer IV iron in outpatient setting?

Historically, the side effect which required most attention during parenteral iron administration has been anaphylactic reaction. While this side effect has been reported more commonly with the high-molecular weight iron dextran, which is rarely used today, patients should be monitored during the administration and through the following 30 minutes as allergic reactions are reported with all IV iron preparations. There is no need to employ premedication for anaphylactic reactions. Headache is the most common side effect which occurs during the early phase of IV administration with all IV iron preparations. Other early phase reactions are reported rarely and include hypotension, muscle cramps, diarrhea, urticaria, fever, nausea, vomiting, hypertension, and chest pain. Lymphadenopathy, myalgia, arthralgia and fever may occur during the late phase. The concerns raised with IV iron administration in HF patients are rather different.[102] Theoretically, overloaded iron -particularly when normal iron reservoirs are full- may deposit in tissues and organs, resulting in adverse biological outcomes. Because iron is a vital compound for bacteria, iron replacement is often assumed to potentially increase the frequency of bacterial infections. Furthermore, iron is thought to increase free radical generation, thereby triggering atherosclerosis.

However, seriousadverse events associated with IV iron therapy are low (approximately <1%) in clinical studies. Life-threatening adverse events are also rare (<0.02%). In studies using ferric sucrose in HF, the main side effect was altered taste with more rare side effects reported as nausea, vomiting, abdominal pain, diarrhea, redness, bronchospasm, fever, myalgia, and injection site reactions. Ferric carboxymaltose was often well-tolerated and no serious allergic reactions were observed. The adverse effects associated with this treatment were mostly mild and included flushing, GIS discomfort, dizziness, rash, erythema, and injection site reactions. No abnormalities were seen in laboratory tests and the most common transient asymptomatic finding was hypophosphatemia.[103]

In a meta-analysis by Avni et al.[104] which included 103 studies with a total of 10,390 patients receiving IV iron treatment, no increase was seen regarding the risk of serious adverse events with IV iron therapy (relative risk [RR], 1.04; 95% CI 0.93–1.17; I(2)=9%). Interestingly, a decreased rate of serious adverse events was noted in HF patients receiving IV iron therapy in a subgroup analysis (RR, 0.45; 95% CI 0.29–0.70; I(2)=0%). The most common side effect seen with IV iron was again infusion reactions, similar to the findings mentioned above (RR 2.47; 95% CI 1.43–4.28; I(2)=0%). Qian et al.[81] conducted a meta-analysis on five key studies of IV iron therapy in HF and did not find an increased risk of cardiovascular events or an increased rate of infections.

In clinical studies, IV iron therapy is often administered in outpatients although in hospital setting. The in-hospital stay may be up to seven hours in some centers with an aim to monitor patients during the infusion as well as the side effects afterwards. Day-time treatment clinics specialized with training in this field may prove useful to facilitate the administration.[105] Furthermore, iron treatment prior to discharge is a reasonable approach in patients hospitalized for acute HF, and studies evaluating this approach are currently ongoing (Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency [Affirm-AHF]; NCT02937454).

8.5 Can we use a combination of intravenous iron and erythropoietin?

The use of erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in chronic kidney

disease has led to considering this approach also for the anemia in HF.

Initially, studies were conducted with a limited number of patients, and the meta-analysis of these studies demonstrated prolonged duration of exertion as well as improvements in the 6-minute walking distance, with improved NYHA class and quality of life.[106] Furthermore, a decrease was observed in hospitalization due to HF and all-cause mortality. The lack of increased adverse events was deemed encouraging to conduct randomized controlled trials with larger number of patients. However, no improvement was observed in clinical outcomes among a total of 2,600 HFrEF patients with hemoglobin levels 9–12 g/dL, while thromboembolic events were increased in the RED-HF study evaluating darbepoetin alfa, a recombinant human erythropoietin.[63] Recent meta-analysis including the RED-HF study have demonstrated improved symptoms and functional capacity with ESA treatment, together with improved quality of life and decreased rate of hospitalization due to HF although an increased risk of thromboembolic events was noted during the safety analysis (RR 1.28, 95% CI 1.03-1.58, p=0.026).[107,108] No increase was observed in terms of serious thromboembolic events. Taking current evidence and high costs into account, ESA treatment is not recommended for the routine treatment of patients with HF.[6]

Other studies have also demonstrated an increased rate of thromboembolic events with ESA treatment. The TREAT study (n=4038) evaluating long-term use of darbepoetin-alfa in diabetic patients with anemia and chronic renal impairment[109] showed a two-fold increase in stroke risk, which led USA Food and Drug Administration (FDA) to issue a warning on chronic renal impairment in 2011 and recommend individual dose adjustment if hemoglobin levels are below 10 g/dL and to initiate treatment with the lowest ESA dose. Findings of this study were consistent with RED-HF.

There is a relatively complex association between erythropoietin and HF. In studies indicating a link between increased erythropoietin and poor prognosis in HF, patients with high levels of erythropoietin are often more anemic.[110] This suggests a peripheral resistance to the effect of endogenous erythropoietin. Pathogenesis of erythropoietin resistance involves iron deficiency, chronic renal impairment, acute and chronic inflammation, cytokines and bone marrow dysfunction. Studies have attempted to explain the increased risk of thromboembolic events with increased number thrombocytes and increased thrombopoietin activity. Both of these conditions are associated with iron deficiency and tend to decrease in dialysis patients receiving IV iron.[111] The fact that baseline erythropoietin levels and post-treatment thrombocyte counts are unknown for the patients in RED-HF as well as those in the TREAT study, and the use of oral preparations for iron replacement (with parenteral iron used more commonly in the placebo group of TREAT) make it more difficult to evaluate the mechanism of the thrombotic effect. It is not possible to draw any conclusions for subjects with baseline hemoglobin levels <9 g/dL as they were excluded in the RED-HF study. There is no consensus regarding the target hemoglobin levels in HF. No difference is seen between ESA and control groups unless hemoglobin values exceed 12 g/dL. The use of fixed and high-dose darbepoetin alfa based on baseline hematocrit values in studies is another aspect of criticism.[112] Therefore, it is warranted to establish optimal hemoglobin levels in HF and to better specify which patients may experience benefit or harm with ESA treatment. When ESA treatment is deemed necessary in HF patients with anemia, iron reservoirs should be screened with laboratory tests and iron replacement should be provided in line with applicable guidelines in the event of iron deficiency.

9.0 OTHER TREATMENT APPROACHES

Dilek Yeşilbursa

9.1 Is oral iron therapy appropriate for the treatment of iron deficiency?

European HF guidelines 2016 recommend iron therapy in HF patients with iron deficiency regardless of the presence or absence of anemia. Oral iron therapy is commonly employed owing to low costs and safety. However, intestinal iron absorption is low in HF. The oral iron used in treatment is often a ferrous salt such as ferrous sulfate (Fe [II]). The oxidation of Fe [II] to Fe [III] causes oxidative damage on mucosa and this local toxicity results in GIS side effects, which are seen in 60% of the patients. Side effects in the form of constipation, dyspepsia, nausea, diarrhea and heartburn are more commonly seen with ferrous sulfate and tend to reduce compliance to treatment. The best iron absorption occurs on empty stomach. However, absorption is decreased as these drugs are usually taken with food due to GIS side effects (Table 15). Side effects resul-

ting from oxidative stress may be prevented by using an oral iron [III]-polymaltose complex.

This allows a controlled and slow release of iron. Furthermore, the structure of oral iron [III]-polymaltose complex reduces the interactions with food and concurrent medications. As a result, use of oral iron therapy appears inappropriate in subjects with disrupted absorption, in patients who cannot tolerate oral treatment and those with poor compliance to treatment owing to the unfavorable effects of oral iron therapy.

The additional factors limiting the intestinal absorption of oral iron preparations in patients with heart failure bring IV iron administration to forefront.[73] One of the key reasons to prefer IV iron therapy is the difficulty of compliance to treatment with oral iron (usually 3 times a day) due to the polypharmacy associated with HF and comorbidities. Another reason is the reduced iron absorption seen in HF owing to several factors such as edema in the intestinal mucosa, ischemia and restricted blood flow (Table 15). Other causes of decreased intestinal absorption include sympathetic nervous system activation, diabetic gastroparesis and use of H2 receptor blockers.

Elevated levels of hepcidin are also among the factors which limit the intestinal absorption of oral iron preparations (Table 15). The proinflammatory cytokines increased in HF augment the hepatic synthesis of hepcidin. Hepcidin is a peptide hormone and the main regulator of systemic iron balance which is essentially synthesized in the liver, found in circulation and excreted by urine.[113,114] Hepcidin decreases iron absorption in the small intestine, interferes with the iron discharge from macrophages when macrophages extract iron from old erythrocytes to release into plasma and interferes with the release of iron into plasma as well as preventing the iron mobilization from hepatic reservoirs. In addition to the negative effect on iron metabolism and the associated hypoferrinemia, hepcidin has also been shown to disrupt erythropoiesis and reduce proliferation and life-span of erythroid precursors in vitro.

The median iron dose required for iron replacement is 1000 mg in HF patients with iron deficiency. The most commonly used oral iron preparation in iron deficiency anemia is ferrous sulfate, with a bioavailability of 10%. The daily dose of ferrous sulfate is 100-200 mg. In the best case scenario where the patient tolerates the daily dose of 200 mg, iron absorption would be 20 mg daily, requiring 50 days to correct iron deficiency. In a less favorable scenario where the intestinal absorption is reduced by half in a patient with HF who can tolerate 100 mg iron daily, only 5% (5 mg) of the iron would be absorbed, requiring 200 days to correct iron deficiency. This period would be even longer in clinical practice owing to the poor compliance in HF patients and reasons such as treatment interruption due to GIS side effects. Therefore, more than 6 months is required to correct iron deficiency using oral iron treatment.

While several cardiologists use oral iron for the treatment of iron deficiency, there is no evidence to support oral iron therapy in HF. Randomized studies comparing erythropoietin with oral iron versus oral iron therapy alone revealed no change in the groups receiving oral iron alone in terms of iron parameters, hemoglobin level, symptom severity and exercise tolerance testing.[64,115,116]

Results of the IRONOUT HF study investigating

Table 15. Reasons to not recommend oral iron therapy in heart failure

Oral iron therapy in heart failure	
Intestinal absorption	Low
	Reduced absorption when taken with food (due to the formulation)
	Reduced absorption when taken with other medications (e.g. phosphate binders, antacids, H2 receptor blockers)
	Elevated hepcidin interfering with iron absorption and release from enterocytes into circulation
	Changes in the gastrointestinal tract in heart failure, such as mucosal edema, local ischemia, perfusion problems
Gastrointestinal side effects	Constipation, dyspepsia, nausea, diarrhea, heartburn (more common with ferrous sulfate)
Compliance	Multiple daily doses (usually 3 times a day)
	Frequency of side effects

the efficacy of oral iron therapy in HF patients with low EF were disclosed in AHA 2016. The 225 patients included in this study were given oral iron polysaccharide twice daily.

At the end of 16 weeks of the randomized, double-blind, placebo-controlled study, no difference was seen in primary (exercise capacity as measured by peak oxygen consumption) and secondary (6-minute walking distance, oxygen kinetics, ventilatory efficiency, quality of life) endpoints.

In light of all such information, oral iron therapy is not recommended for the treatment of iron deficiency in HF with or without anemia.

9.2 Could blood transfusion be a treatment option for anemia?

Transfusion is the only way of increasing hemoglobin levels and thereby tissue oxygenation rapidly. Blood transfusion is used as an acute treatment and offers only transient benefits. On the other hand, it is associated with several risks (immune system suppression, infection risk, iron overload, HLA sensitization, etc.). Therefore, it should be reserved for hospitalized patients with deep anemia in order to avoid side effects of transfusion. It is recommended to initially treat the correctable factors (iron, folate and/or vitamin B12 deficiency, etc.) which may be the underlying cause of anemia in anemic patients with HF.

There is no specific hemoglobin value specified as a threshold for transfusion. Although the evidence level is low, red blood cell transfusion should usually be considered when hemoglobin level is <7–8 g/dL in asymptomatic patients or when hematocrit value is <30%. In symptomatic patients if the symptoms are related to the anemia, transfusion may be administered when hemoglobin levels are <10 g/dL.

There is no large, randomized controlled trial evaluating the effect of transfusions given when hemoglobin levels are <8 g/dL or <10 g/dL in patients with stable or decompensated HF. A meta-analysis of 26 observational studies and 6 studies with low evidence level demonstrated no improvement with the liberal transfusion protocol compared to the less aggressive transfusion protocol in terms of short-term mortality in heart failure patients with anemia.[117]

Transfusion is employed to increase the blood's oxygen-carrier capacity and to provide improved oxygenation for the cells. However, the oxygen-carrier capacity of blood supplied from blood banks is known to be reduced in proportion to the length of storage time. This is a result of the decreased 2,3 diphosphoglycerate (DPG) in the blood. Low DPG levels increase the oxygen affinity of hemoglobin and restrict the oxygen release into tissues.

When using redblood cell transfusion in patients with heart failure, it is recommended to assess the patient's volume status and to adjust transfusion rate and administer additional diuretics in order to avoid volume overload.

9.3 Do erythropoietin preparations play a role in treatment?

Erythropoietin is a glycoprotein hormone primarily produced in the kidney by peritubular fibroblasts. It is released in response to hypoxia and stimulates the erythroid cell proliferation essentially by preventing apoptosis in erythroid precursors in the bone marrow. Studies have shown decreased erythropoietin levels with renal dysfunction in one third of HF patients with anemia.[118] On the other hand, other studies have reported severely poor clinical outcomes in patients with high levels of endogenous erythropoietin.[119] Furthermore, no correlation has been found between hemoglobin and erythropoietin levels. These findings indicate resistance to endogenous erythropoietin in the bone marrow in addition to reduced endogenous erythropoietin synthesis in HF patients with anemia.[118]

Chronic kidney disease is common among patients with HF and is associated with decreased erythropoietin production in the kidneys. Renal damage is primarily associated with hemodynamic disorders and parenchymal damage. Hemodynamic changes result from the redistribution of intrarenal blood flow and reduced renal blood flow leading to hypoxic renal damage. Parenchymal damage, on the other hand, is associated with tubulointerstitial fibrosis, tubular loss and glomerulosclerosis. Both the hemodynamic and parenchymal disorders contribute to reduced erythropoietin production.[118]

Elevated levels of several proinflammatory cytokines such as tumor necrosis factor-alfa and IL-6 are seen in patients with heart failure. Cytokines reduce erythropoietin synthesis in the kidney by means of several mediators and suppress the bone marrow response. Among proinflammatory cytokines, IL-6 increases the hepatic synthesis of hepcidin. Hepcidin is a peptide hormone synthesized in the liver and is the

main regulator of systemic iron balance. It inhibits intestinal iron absorption as well as iron release from macrophages by binding to ferroportin.

Hepcidin also suppresses erythropoietin production and causes erythropoietin resistance by suppressing the proliferation of erythroid precursors in bone marrow. Consequently, erythropoietin insufficiency or bone marrow unresponsiveness despite presence of adequate erythropoietin occurs in anemic HF patients.

The use of erythropoiesis-stimulating agents for the treatment of anemia in chronic kidney disease has led to considering this approach also for the anemia in HF. Darbepoetin alfa is a recombinant human erythropoietin. It also contains a carbohydrate chain which prolongs the half-life and increases biological activity as well as receptor affinity.

In 2000, Silverberg et al. were the first to report favorable outcomes with erythropoietin and IV iron therapy in 26 patients with severe HF and anemia.[120] This retrospective study revealed improved NYHA class, increased EF values, reduced rates of hospitalization and decreased need for diuretics in patients treated with IV iron and erythropoietin. Similar results were reported in a randomized, open-label study conducted by the same investigators 1 year later.[121] Palazzuoli et al. reported increased hemoglobin values and improved NYHA class as well as favorable effects on EF, exercise capacity and BNP levels with erythropoietin treatment.[122] While increased hemoglobin levels and improved quality of life were observed in a randomized, placebo-controlled study with darbepoetin, no difference was seen in terms of peak oxygen consumption, exercise duration, BNP and renal functions (Table 16).

Although favorable outcomes were reported, these study results are not broadly applicable owing to the limited number of patients enrolled in the studies. Furthermore, these small-scale randomized studies have not evaluated hard clinical outcomes such as all-cause mortality as primary endpoints. Limitations of these studies include limited sample size, short duration and lack of double-blind design. The double-blind, placebo-controlled study by van Veldhuisen et al. found moderately increased hemoglobin levels with darbepoetin treatment in 165 anemic HF patients; however, no change was seen in quality of life, NYHA class and exercise capacity parameters.[116] Two large, multi-center, double blind, placebo-controlled studies investigating darbepoetin (STAMINA-HF and RED-HF) revealed no improvement in terms of hospitalization or mortality (Table 16).

In STAMINA-HF, 319 patients with HF (EF 40%) and hemoglobin levels 9-12.5 g/dL received darbepoetin alfa or placebo every two weeks for 1 year with a target hemoglobin level of 14±1 g/dL.[64] The primary endpoint of the study was the change in treadmill exercise duration while change in NYHA class and quality of life were evaluated as secondary endpoints. All-cause mortality and HF hospitalization were also evaluated. Although increased hemoglobin values up to median 1.8 g/dL were seen with darbepoetin, no improvement was observed in terms of exercise duration, quality of life and NYHA class. A non-significant decreasing trend was seen for all-cause mortality and first HF hospitalization (HR 0.68; 95% CI 0.43–1.08; p=0.10). Other adverse effects such as hypertension and myocardial infarction were found to be similar between the two groups.

RED-HF, the largest erythropoietin study to date is a double-blind, randomized, placebo-controlled, multi-center study investigating darbepoetin alfa in patients with HF.[63] In this study, a total of 2278 patients with HF (NYHA class II-IV, EF <40%) and hemoglobin levels 9-12 g/dL treated with darbepoetin alfa or placebo (Table 16). At 28 months of follow-up, hemoglobin levels were observed to increase from 11.2 g/dL to 13 g/dL in the treatment group while there was no change in the placebo group. No difference was seen between the two groups regarding the primary endpoint which consisted of all-cause death or first hospitalization (50.7% vs 49.5%, HR 1.01; 95% CI 0.90–1.13; p=0.87). Furthermore, no benefit was noted in other secondary endpoints including all-cause mortality, cardiovascular death, HF hospitalization and coronary events. On the other hand, an increased rate of thromboembolic events was observed in the treatment group compared to placebo (13.5% and 10.0; p=0.01). Stroke risk was found to be higher in the darbepoetin alfa group (5.4% vs 3.9%).

Two meta-analyses which did not include the RED-HF study demonstrated significant improvement in quality of life, exercise tolerance and NYHA class with a decreased rate of HF hospitalization among patients treated with erythropoietin.[106,123] Further meta-analyses including RED-HF are necessary to establish the benefit/risk profile of treatment with erythropoietin.

Table 16. Studies on erythropoiesis-stimulating agents in heart failure patients with anemia

Study	Study Design	N	ESA / control	Iron	Follow-up (months)	Endpoint	Result
Silverberg et al., 2000		26	Epo	Yes (IV)	7±5	NYHA class, LVEF, decrease diuretics dose, hospitalization	Improvement in NYHA class, increased EF, decrease in hospitalization rates and reduced need for diuretics
Silverberg et al., 2001	Single-center, randomized, open-label	32	Epoetin alfa	Yes (IV)	8.2	NYHA class, LVEF, decrease diuretics dose, hospitalization	Improvement in NYHA class with increased Hb levels, increase in EF, decreased hospitalization rates and reduced need for diuretics
Mancini et al., 2003	Single-center, randomized, single-blind	23	Epoetin alfa/placebo	Yes	3	Exercise capacity, vasodilator function	Increase in 6-MWD and peak oxygen consumption with increased Hb levels
Palazzuoli et al., 2007	Single-center, randomized, double-blind	51	Epopoetin beta/placebo	Yes	12	Primary: LV dimensions, LVEF, Hb, Cr, BNP Secondary: Cardiac event (sudden death, hospitalization, MI), weight, edema, NYHA class	Decrease in LV size, volume and mass; increased EF; reduction in PAP and BNP; decreased hospitalization, increased Hb in the EPO group
Ponilkowski et al., 2007	Multi-center, randomized, double-blind	41	Darbepoetin alfa/placebo	Yes	6	Primary: Exercise capacity Secondary: Change in peak VO2, exercise capacity, Hb, NYHA class, quality of life, BNP, weight, hospitalization	No difference between the groups in terms of VO2, exercise duration, BNP and renal function
Van Veldhuisen 2007	Multi-center, randomized, double-blind	165	Darbopoetin alfa/placebo	Yes	6	Primary: Increase in Hb, Secondary: LVEF, 6-MWT, NYHA, quality of life, PGA	Non-significant between the two groups in terms of 6-MWD (p=0.074) and PGA (p=0.057)
Ghali et al., 2008 STAMİNA-HeFT	Multi-center, randomized, double-blind	319	Darbopoetin alfa/placebo	Yes	12	Primary: Change in exercise tolerance Secondary: NYHA, quality of life, time to death, first hospitalization due to HF	No significant improvement in exercise duration, NYHA and quality of life with darbepoetin compared to placebo
Swedberg et al., 2013 RED-HF	Multi-center, randomized, double-blind	2278	Darbopoetin alfa/placebo	Yes	28	Primary: All-cause mortality or first hospitalization due to HF Secondary: Death from cardiovascular cause or first hospitalization due to HF, MI, stroke, hospitalization due to HF, sudden death, quality of life	No significant difference in primary endpoints between the two groups. Increased rate of thromboembolic events in the treatment group.

LV: Left ventricle; EF: Ejection fraction; Hb: Hemoglobin; 6-MWD: Six-minute walking distance; HF: Heart failure; MI: Myocardial infarction; Cr: Creatinine, PGA: Patient's Global Assessment score.

The differences between the studies may be partially explained by the different protocols employed, different doses of erythropoietin and different grades of anemia.

Vast majority of anemic HF patients have concurrent renal dysfunction. Currently, erythropoietin is recommended for the treatment of anemia in patients with chronic kidney disease. Could it also be used in anemic HF patients with renal dysfunction? Different doses and routes of administration (oral iron vs. IV iron) used for iron treatment with erythropoietin in different studies may notably affect the outcomes (owing to the defective oral iron absorption in patients with heart failure). Atrial fibrillation and hypertension often co-exist with HF. These conditions may increase the rate of embolic events. The hemoglobin level to initiate treatment with erythropoietin has been specified as 11.5 g/dL in large studies. This hemoglobin level may not be an appropriate target to initiate erythropoietin treatment. The darbepoetin dose used in studies may be high. Further studies are warranted to find out the answer to all these questions (optimal hemoglobin target for intervention, clinical characteristics of the patients, comorbidities to avoid erythropoietin treatment).

However, current guidelines do not recommend the use of erythropoietin preparations for the treatment of anemia in HF.

10.0 CONSIDERATIONS FROM THE HEMATOLOGICAL POINT OF VIEW

Mustafa Çetiner

10.1 How reliable are ferritin and transferrin saturation as criteria for iron deficiency diagnosis?

While serum ferritin levels and TSAT are the most commonly utilized and most accurate tests for the diagnosis of iron deficiency, they are limited in terms of definitive diagnostic values. Serum ferritin is an acute phase reactant which increases in the presence of inflammation. Also, ferritin levels are known to potentially differ between males and females. Similar conditions also apply to TSAT. TSAT is calculated by two different methods in practice. The first method defines TSAT as the serum iron:iron binding capacity ratio. (TSAT = (Serum iron/Total iron binding capacity) × 100). This is the commonly utilized method.

The second method employs serum transferrin levels which enable iron transfer in the plasma while calculating the TSAT value (Serum iron/Serum transferrin x 70.9).[124] Serum transferrin is a protein which decreases with malnutrition and chronic disease. Therefore, it tends to be elevated in chronic inflammation and chronic diseases where serum iron levels remain unchanged. This value may also demonstrate fluctuations.[125]

Taken together, serum ferritin and TSAT may provide incorrect results and mask iron deficiency particularly in the presence of chronic disease, inflammation and infection. This risk may be even more misleading with the standalone iron deficiency which develops without anemia, representing increasingly more significance from the current clinical perspective.

Studies show that a TSAT value below 20% provides a good indicator of iron deficiency.[48] However, there is no definite "cut-off" value for ferritin. Some studies indicate that iron deficiency cannot be ruled out when ferritin levels are below 100 ng/mL or even 200 μg/L.[126,127]

In recent years, the "soluble" transferrin receptor (sTfR) has become another test utilized for the diagnosis of iron deficiency owing to its early and high sensitivity.[128] The transferrin receptor is a membrane protein which allows internalization of iron into the cell. During this internalization process, some of the TfRs are shed into circulation, which may be measured as sTfR.[129] Elevated sTfR levels are seen in iron deficiency and these elevated levels are not influenced by chronic disease, infection or inflammation. Owing to this advantage, sTfR may be a more accurate test especially in the presence of chronic disease anemia or in patients with infection and inflammation (Table 17). However, it should be noted that false decreases may be seen with this value in the event of malnutrition or atransferrinemia.[130] Generally, in microcytic anemias with MCV below 75 fL, sTfR level assay is recommended for the differential diagnosis between iron deficiency and anemias secondary to chronic inflammation or chronic disease anemia. The fact that this is a new test associated with high costs and difficulty in standardization poses a barrier regarding its widespread use as a standard method. One may expect to see this test in standard practice during the years to come.[130]

Iron staining of bone marrow biopsy material remains the method with the highest level of accuracy in showing iron deficiency and iron reservoirs.

Table 17. Tests which may be used for the differential diagnosis of iron deficiency anemia

Test	Iron deficiency anemia	Chronic disease anemia	Iron deficiency anemia + chronic disease anemia
Ferritin	Low	High	Normal / high
TIBC	High	Low	Normal / high
SI	Low	Low	Low
sTfR	High	Normal	High

TIBC: Total iron binding capacity; SI: Serum iron; sTfR: Soluble transferrin receptor.

10.2 How is the differential diagnosis established in iron deficiency and anemia versus other anemias?

Taking into account the fact that patients with heart failure are often elderly, the anemia seen in these patients may result from various causes. Evaluating the parameters presented in Table 17 is important for the differential diagnosis of iron deficiency anemia and other anemias.[131] Low hemoglobin level is one of the parameters which have direct effects on life expectancy in patients over the age of sixty five years. Studies show increased frequency and length of hospitalization as well as higher mortality rates in older anemic patients.[132] Therefore, it is essential to probe and treat anemia in the elderly.

Chronic disease anemia, chronic inflammation, chronic infections, myelodysplastic syndrome-like bone marrow failure syndromes, hematological cancers, bone marrow involvement of non-hematological cancers, drug effects, deficiency of other essential components such as vitamin B12 and folic acid should also be taken into account as well as iron deficiency when considering the causes of anemia. Hematology consultation is recommended for patients for whom anemia etiology cannot be adequately clarified with standard tests.

10.3 How safe is intravenous iron therapy? Could it cause toxic effects?

Intravenous iron therapies have remained as treatments used with concern owing to the serious risk of anaphylaxis associated with IV iron preparations containing dextran.[133,134] Therefore, dextran-containing molecules are not preferred in the current practice while preparations which do not contain dextran such as iron sucrose and iron carboxymaltose are used instead.

Risk of allergic reaction is the most important side effect to discuss regarding the drugs in this group. Traditionally, using anti-histamines prior to IV iron administration has been a widely adopted approach. However, this approach is in fact not recommended. Contrary to the popular belief, diphenhydramine and similar agents used for this purpose mildly increase the risk of allergic reactions and infusion reactions, and also lead to a greater risk of nasal congestion, wheezing and supraventricular tachycardia.[135] Premedication should not be used except for patients with history of drug allergy or asthma, and these patients should be given 125 mg methylprednisolone prior to administration.[135]

As stated above, anaphylaxis is the most important side effect associated with IV iron therapy. Hypersensitivity risks of IV iron preparations are presented in Table 18.[136,137]

There is also a reaction referred to as Fishbane reaction which may be confused with hypersensitivity reactions following the administration of intravenous iron treatment.[138] This reaction is characterized by mild chest and back pain, arthralgia, and myalgia. The key

Table 18. Frequency of life-threatening drug reactions with IV iron preparations

	Risk in one million individuals
High-molecular weight dextran	11.3
Low-molecular weight dextran	3.3
Iron gluconate (not available in Turkey)	0.9
Iron sucrose	0.6
Iron carboxymaltose	A similar risk has been observed in comparative studies with iron sucrose[137]

feature of this presentation is the absence of tachycardia and hypotension.

In fact, hypotension, tachycardia, bronchoconstriction, stridor, and periorbital edema may be observed with true hypersensitivity reactions. Fishbane reaction does not require medical intervention and the presentation resolves spontaneously within minutes. As the anxiety the patient or the physician may experience during this period may hinder completing the administration, the team in charge of IV iron treatment should be informed about Fishbane reaction.

The report on IV iron administration issued by EMA in 2013[139] has clearly identified the principles to be followed during the administration. These principles are summarized in Table 19.

Conditions associated with an increased frequency of allergic reactions are well-documented.[140] These risk groups are presented in Table 20.

In fact, a very low risk of hypersensitivity is reported in clinical studies, particularly with non-dextran containing preparations. This risk is not higher than it is with any other drug. The total risk of hypersensitivity reaction development was found to be 24-68 in one hundred thousand individuals through 688,183 IV iron administrations.[141]

A meta-analysis evaluating the data from one hundred and three studies has compared the use of oral iron and placebo, and did not find any side effects which increase with the use of IV iron agents. While GIS side effects were significantly low with IV preparations, allergic reactions were increased although no death was reported in these patients.[104]

Table 19. Principles to follow during IV iron administration

A test dose for IV preparations is neither necessary nor recommended by EMA and FDA.
Patients should remain under monitoring for at least 30 minutes after the administration. Hypersensitivity reactions often occur during or within half an hour after the administration.
IV administration must not be performed in subjects with history of hypersensitivity reaction during IV iron treatment.
The administration should be employed with caution in patients with known allergy (drug allergy), serious atopy, systemic inflammatory response, rheumatoid arthritis or any other systemic inflammatory disease.
The administration should be performed by an experienced team and in a setting where interventions are readily available.

Table 20. IV demir uygulaması sırasında aşırı duyarlılık riskinin arttığı durumlar

Rapid administration*
Subjects with history of drug reaction or hypersensitivity reaction
Subjects with serious asthma or eczema
Mastocytosis
Subjects with serious respiratory or cardiac condition**
Patients receiving ACE inhibitors or beta blockers**
Pregnancy (first trimester)***
Subjects with systemic inflammatory conditions (systemic inflammatory response, rheumatoid arthritis)
Intense anxiety experienced by the relevant healthcare professional, physician or patient****

**Rapid administration is often discouraged. However, this is not the case for carboxymaltose. IV carboxymaltose administration should not exceed 20-30 minutes and the fluid volume should be no more than 250 mL. Prolonged administration and over-dilution impair the drug's stability and increase the risk of reactions.*

***Rapid decompensation may be observed following Fishbane-type reactions in this group of patients and clinical symptoms may present with a rapid and more dramatic prognosis due to limited organ capacity.*

****Administration during the first trimester is not common due to the lack of sufficient clinical data.*

*****Intense anxiety may trigger Fishbane-type reactions. A potential hypersensitivity reaction may worsen the clinical presentation and complicate the management.*

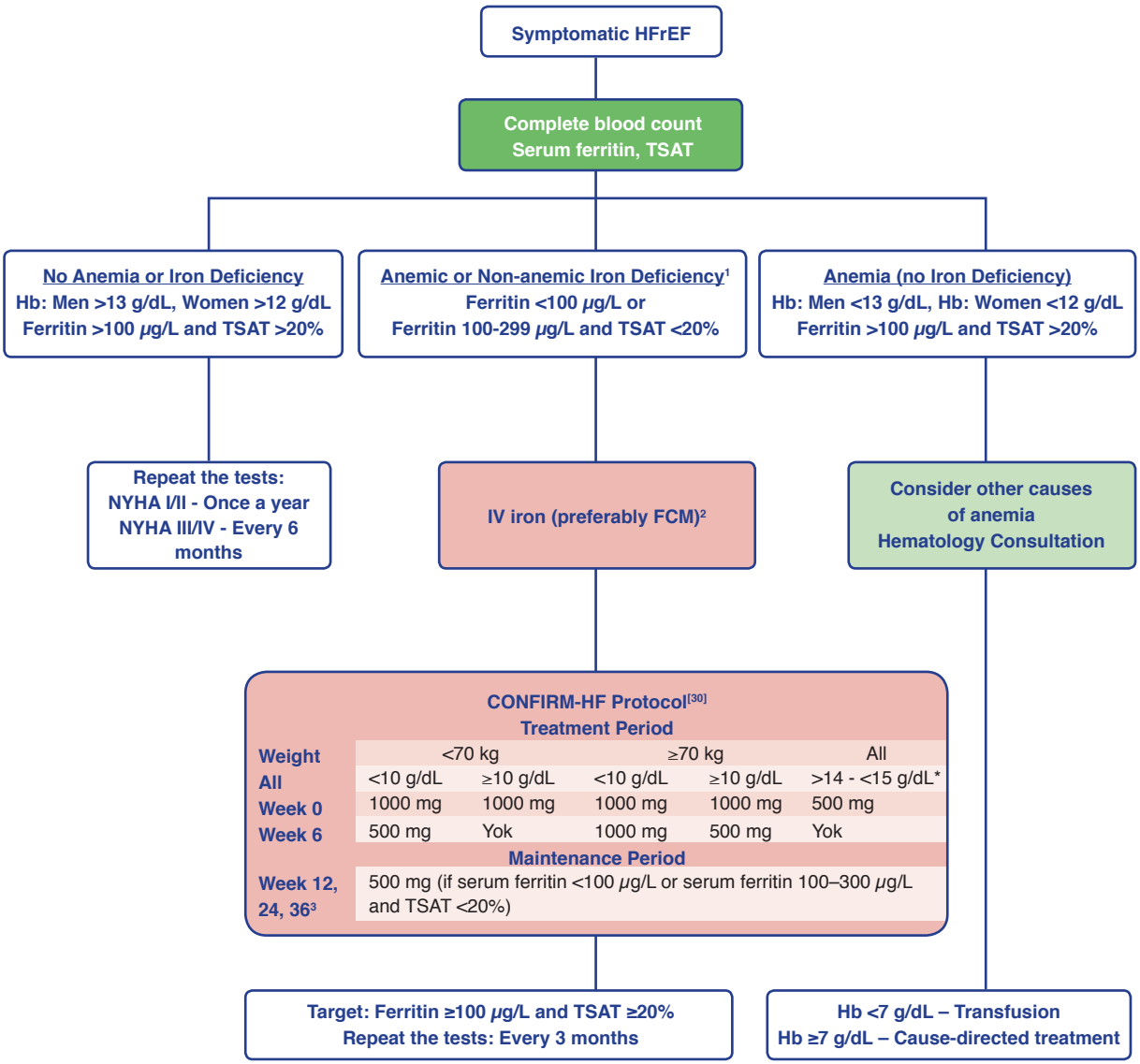
The fact that bacteria and other infectious agents require iron as a growth factor and the increased frequency of infections in patients diagnosed with hereditary hemochromatosis with increased iron load[142] suggest a link between IV iron load and frequency of infections. However, no such link has been demonstrated in studies.

Nausea, vomiting, and diarrhea may occur in patients receiving treatment with IV iron, although at a much lower rate compared to those receiving oral iron therapies. Tinnitus, headache, pruritus, rash, and urticaria may also occur. The likelihood varies from 6% to 10% for each of these symptoms. Only nausea occurs with an incidence of 10-15% and is highlighted as the most common side effect. All of these side effects are temporary.[143]

Iron overload is observed very rarely and does not occur with standard treatments.

11.0 CONSENSUS ALGORITHM

Diagnosis and treatment of iron deficiency in chronic heart failure



FCM: Ferric carboxymaltose; Hb: Hemoglobin; TSAT: Transferrin saturation

[1]Iron deficiency diagnosis is irrespective of anemia. Iron deficiency diagnosis in heart failure should be based on the criteria specified in the algorithm provided above. On the other hand, it should be taken into account that ferritin values <30 μg/L and transferrin saturation <20% are required for the definitive diagnosis of classic iron deficiency. However, because ferritin is an acute phase reactant, iron deficiency cannot be ruled out with levels of 30–100 μg/L. In recent years, where available, transferrin receptor-1 (TfR-1) level has been used for the diagnosis of iron deficiency as a marker which is not influenced by infection or inflammation. Ferritin index (TfR-1/log ferritin) <1 translates into a diagnosis of iron deficiency.

[2]Treatment decision is independent from anemia. In practice, the iron to be administered as 500 mg or 1000 mg is recommended to be given as an infusion >15 minutes after dilution in 250 mL of 0.9% NaCl. Although iron was administered as intravenous bolus >1 minute without reconstitution in the CONFIRM-HF study, intravenous bolus administration is associated with a risk of necrosis due to potential extravasation and therefore the consensus algorithm herein recommends administering iron as infusion after dilution.

[3]There is no evidence on the benefit of continued iron therapy after 36 weeks.

*Iron therapy is not recommended when Hb >15 g/dL as efficacy and safety have not been established.

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